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(71) Applicants *(for all designated States except US)*: **SMITHKLINE BEECHAM CORPORATION** [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US). **SMITHKLINE BEECHAM P.L.C.** [GB/GB]; New Horizons Court, Great West Road, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **AGARWAL, Pankaj** [IN/US]; 251 West DeKalb Pike, King of Prussia, PA 19406 (US). **MURDOCH, Paul, R.** [GB/GB]; New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **RIZVI, Safia, K.** [PK/US]; 4617 Pine Street, Philadelphia, PA 19143 (US). **SMITH, Randall, F.** [US/US]; 4138 Presidential Drive, Lafayette Hill, PA 19444 (US). **XIANG, Zhaoying** [CN/US]; 2413 Ridgeway, Fort Lee, NJ 07024 (US).

(74) Agents: **GIMMI, Edward, R.** et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

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(54) Title: NOVEL COMPOUNDS

(57) Abstract: Polypeptides and polynucleotides of the genes set forth in Table I and methods for producing such polypeptides by recombinant techniques are disclosed. Also disclosed are methods for utilizing polypeptides and polynucleotides of the genes set forth in Table I in diagnostic assays.

Novel Compounds

Field of Invention

This invention relates to newly identified polypeptides and polynucleotides encoding such polypeptides, to their use in diagnosis and in identifying compounds that may be agonists, antagonists that are potentially useful in therapy, and to production of such polypeptides and polynucleotides. The polynucleotides and polypeptides of the present invention also relate to proteins with signal sequences which allow them to be secreted extracellularly or membrane-associated (hereinafter often referred collectively as secreted proteins or secreted polypeptides).

Background of the Invention

The drug discovery process is currently undergoing a fundamental revolution as it embraces "functional genomics", that is, high throughput genome- or gene-based biology. This approach as a means to identify genes and gene products as therapeutic targets is rapidly superseding earlier approaches based on "positional cloning". A phenotype, that is a biological function or genetic disease, would be identified and this would then be tracked back to the responsible gene, based on its genetic map position.

Functional genomics relies heavily on high-throughput DNA sequencing technologies and the various tools of bioinformatics to identify gene sequences of potential interest from the many molecular biology databases now available. There is a continuing need to identify and characterise further genes and their related polypeptides/proteins, as targets for drug discovery.

Proteins and polypeptides that are naturally secreted into blood, lymph and other body fluids, or secreted into the cellular membrane are of primary interest for pharmaceutical research and development. The reason for this interest is the relative ease to target protein therapeutics into their place of action (body fluids or the cellular membrane). The natural pathway for protein secretion into extracellular space is the endoplasmic reticulum in eukaryotes and the inner membrane in prokaryotes (Palade, 1975, Science, 189, 347; Milstein, Brownlee, Harrison, and Mathews, 1972, Nature New Biol., 239, 117; Blobel, and Dobberstein, 1975, J. Cell. Biol., 67, 835). On the other hand, there is no known natural pathway for exporting a protein from the exterior of the cells into the cytosol (with the exception of pinocytosis, a mechanism of snake venom toxin intrusion into cells). Therefore targeting protein therapeutics into cells poses extreme difficulties.

The secreted and membrane-associated proteins include but are not limited to

all peptide hormones and their receptors (including but not limited to insulin, growth hormones, chemokines, cytokines, neuropeptides, integrins, kallikreins, lamins, melanins, natriuretic hormones, neuropsin, neurotropins, pituitiary hormones, pleiotropins, prostaglandins, secretogranins, selectins, thromboglobulins, thymosins), the breast and colon cancer gene products, leptin, the obesity gene protein and its receptors, serum albumin, superoxide dismutase, spliceosome proteins, 7TM (transmembrane) proteins also called as G-protein coupled receptors, immunoglobulins, several families of serine proteinases (including but not limited to proteins of the blood coagulation cascade, digestive enzymes), deoxyribonuclease I, etc.

Therapeutics based on secreted or membrane-associated proteins approved by FDA or foreign agencies include but are not limited to insulin, glucagon, growth hormone, chorionic gonadotropin, follicle stimulating hormone, luteinizing hormone, calcitonin, adrenocorticotropic hormone (ACTH), vasopressin, interleukines, interferones, immunoglobulins, lactoferrin (diverse products marketed by several companies), tissue-type plasminogen activator (Alteplase by Genentech), hyaulorindase (Wydase by Wyeth-Ayerst), dornase alpha (Pulmozyme\ by Genentech), Chymodiactin (chymopapain by Knoll), alglucerase (Ceredase by Genzyme), streptokinase (Kabikinase by Pharmacia) (Streptase by Astra), etc. This indicates that secreted and membrane-associated proteins have an established, proven history as therapeutic targets. Clearly, there is a need for identification and characterization of further secreted and membrane-associated proteins which can play a role in preventing, ameliorating or correcting dysfunction or disease, including but not limited to diabetes, breast-, prostate-, colon cancer and other malignant tumors, hyper- and hypotension, obesity, bulimia, anorexia, growth abnormalities, asthma, manic depression, dementia, delirium, mental retardation, Huntington's disease, Tourette's syndrome, schizophrenia, growth, mental or sexual development disorders, and dysfunctions of the blood cascade system including those leading to stroke. The proteins of the present invention which include the signal sequences are also useful to further elucidate the mechanism of protein transport which at present is not entirely understood, and thus can be used as research tools.

Summary of the Invention

The present invention relates to particular polypeptides and polynucleotides of the genes set forth in Table I, including recombinant materials and methods for their production. Such polypeptides and polynucleotides are of interest in relation to methods of treatment of

certain diseases, including, but not limited to, the diseases set forth in Tables III and V, hereinafter referred to as "diseases of the invention". In a further aspect, the invention relates to methods for identifying agonists and antagonists (*e.g.*, inhibitors) using the materials provided by the invention, and treating conditions associated with imbalance of polypeptides and/or polynucleotides of the genes set forth in Table I with the identified compounds. In still a further aspect, the invention relates to diagnostic assays for detecting diseases associated with inappropriate activity or levels the genes set forth in Table I. Another aspect of the invention concerns a polynucleotide comprising any of the nucleotide sequences set forth in the Sequence Listing and a polypeptide comprising a polypeptide encoded by the nucleotide sequence. In another aspect, the invention relates to a polypeptide comprising any of the polypeptide sequences set forth in the Sequence Listing and recombinant materials and methods for their production. Another aspect of the invention relates to methods for using such polypeptides and polynucleotides. Such uses include the treatment of diseases, abnormalities and disorders (hereinafter simply referred to as diseases) caused by abnormal expression, production, function and or metabolism of the genes of this invention, and such diseases are readily apparent by those skilled in the art from the homology to other proteins disclosed for each attached sequence. In still another aspect, the invention relates to methods to identify agonists and antagonists using the materials provided by the invention, and treating conditions associated with the imbalance with the identified compounds. Yet another aspect of the invention relates to diagnostic assays for detecting diseases associated with inappropriate activity or levels of the secreted proteins of the present invention.

Description of the Invention

In a first aspect, the present invention relates to polypeptides the genes set forth in Table I. Such polypeptides include:

(a) an isolated polypeptide encoded by a polynucleotide comprising a sequence set forth in the Sequence Listing, herein when referring to polynucleotides or polypeptides of the Sequence Listing, a reference is also made to the Sequence Listing referred to in the Sequence Listing;

(b) an isolated polypeptide comprising a polypeptide sequence having at least 95%, 96%, 97%, 98%, or 99% identity to a polypeptide sequence set forth in the Sequence Listing;

(c) an isolated polypeptide comprising a polypeptide sequence set forth in the Sequence Listing;

(d) an isolated polypeptide having at least 95%, 96%, 97%, 98%, or 99% identity to a polypeptide sequence set forth in the Sequence Listing;

(e) a polypeptide sequence set forth in the Sequence Listing; and

(f) an isolated polypeptide having or comprising a polypeptide sequence that has an Identity Index of 0.95, 0.96, 0.97, 0.98, or 0.99 compared to a polypeptide sequence set forth in the Sequence Listing;

(g) fragments and variants of such polypeptides in (a) to (f).

Polypeptides of the present invention are believed to be members of the gene families set forth in Table II . They are therefore of therapeutic and diagnostic interest for the reasons set forth in Tables III and V. The biological properties of the polypeptides and polynucleotides of the genes set forth in Table I are hereinafter referred to as "the biological activity" of polypeptides and polynucleotides of the genes set forth in Table I. Preferably, a polypeptide of the present invention exhibits at least one biological activity of the genes set forth in Table I.

Polypeptides of the present invention also include variants of the aforementioned polypeptides, including all allelic forms and splice variants. Such polypeptides vary from the reference polypeptide by insertions, deletions, and substitutions that may be conservative or non-conservative, or any combination thereof. Particularly preferred variants are those in which several, for instance from 50 to 30, from 30 to 20, from 20 to 10, from 10 to 5, from 5 to 3, from 3 to 2, from 2 to 1 or 1 amino acids are inserted, substituted, or deleted, in any combination.

Preferred fragments of polypeptides of the present invention include an isolated polypeptide comprising an amino acid sequence having at least 30, 50 or 100 contiguous amino acids from an amino acid sequence set forth in the Sequence Listing, or an isolated polypeptide comprising an amino acid sequence having at least 30, 50 or 100 contiguous amino acids truncated or deleted from an amino acid sequence set forth in the Sequence Listing. Preferred fragments are biologically active fragments that mediate the biological activity of polypeptides and polynucleotides of the genes set forth in Table I, including those with a similar activity or an improved activity, or with a decreased undesirable activity. Also preferred are those fragments that are antigenic or immunogenic in an animal, especially in a human.

Fragments of a polypeptide of the invention may be employed for producing the corresponding full-length polypeptide by peptide synthesis; therefore, these variants may be employed as intermediates for producing the full-length polypeptides of the invention. A polypeptide of the present invention may be in the form of the “mature” protein or may be a part of a larger protein such as a precursor or a fusion protein. It is often advantageous to include an additional amino acid sequence that contains secretory or leader sequences, pro-

sequences, sequences that aid in purification, for instance multiple histidine residues, or an additional sequence for stability during recombinant production.

Polypeptides of the present invention can be prepared in any suitable manner, for instance by isolation form naturally occurring sources, from genetically engineered host cells comprising expression systems (*vide infra*) or by chemical synthesis, using for instance automated peptide synthesizers, or a combination of such methods. Means for preparing such polypeptides are well understood in the art.

In a further aspect, the present invention relates to polynucleotides of the genes set forth in Table I. Such polynucleotides include:

(a) an isolated polynucleotide comprising a polynucleotide sequence having at least 95%, 96%, 97%, 98%, or 99% identity to a polynucleotide sequence set forth in the Sequence Listing;

(b) an isolated polynucleotide comprising a polynucleotide set forth in the Sequence Listing;

(c) an isolated polynucleotide having at least 95%, 96%, 97%, 98%, or 99% identity to a polynucleotide set forth in the Sequence Listing;

(d) an isolated polynucleotide set forth in the Sequence Listing;

(e) an isolated polynucleotide comprising a polynucleotide sequence encoding a polypeptide sequence having at least 95%, 96%, 97%, 98%, or 99% identity to a polypeptide sequence set forth in the Sequence Listing;

(f) an isolated polynucleotide comprising a polynucleotide sequence encoding a polypeptide set forth in the Sequence Listing;

(g) an isolated polynucleotide having a polynucleotide sequence encoding a polypeptide sequence having at least 95%, 96%, 97%, 98%, or 99% identity to a polypeptide sequence set forth in the Sequence Listing;

(h) an isolated polynucleotide encoding a polypeptide set forth in the Sequence Listing;

(i) an isolated polynucleotide having or comprising a polynucleotide sequence that has an Identity Index of 0.95, 0.96, 0.97, 0.98, or 0.99 compared to a polynucleotide sequence set forth in the Sequence Listing;

(j) an isolated polynucleotide having or comprising a polynucleotide sequence encoding a polypeptide sequence that has an Identity Index of 0.95, 0.96, 0.97, 0.98, or 0.99 compared to a polypeptide sequence set forth in the Sequence Listing; and

polynucleotides that are fragments and variants of the above mentioned polynucleotides or that are complementary to above mentioned polynucleotides, over the entire length thereof.

Preferred fragments of polynucleotides of the present invention include an isolated polynucleotide comprising an nucleotide sequence having at least 15, 30, 50 or 100

contiguous nucleotides from a sequence set forth in the Sequence Listing, or an isolated polynucleotide comprising a sequence having at least 30, 50 or 100 contiguous nucleotides truncated or deleted from a sequence set forth in the Sequence Listing.

Preferred variants of polynucleotides of the present invention include splice variants, allelic variants, and polymorphisms, including polynucleotides having one or more single nucleotide polymorphisms (SNPs).

Polynucleotides of the present invention also include polynucleotides encoding polypeptide variants that comprise an amino acid sequence set forth in the Sequence Listing and in which several, for instance from 50 to 30, from 30 to 20, from 20 to 10, from 10 to 5, from 5 to 3, from 3 to 2, from 2 to 1 or 1 amino acid residues are substituted, deleted or added, in any combination.

In a further aspect, the present invention provides polynucleotides that are RNA transcripts of the DNA sequences of the present invention. Accordingly, there is provided an RNA polynucleotide that:

(a) comprises an RNA transcript of the DNA sequence encoding a polypeptide set forth in the Sequence Listing;

(b) is a RNA transcript of a DNA sequence encoding a polypeptide set forth in the Sequence Listing;

(c) comprises an RNA transcript of a DNA sequence set forth in the Sequence Listing; or

(d) is a RNA transcript of a DNA sequence set forth in the Sequence Listing; and RNA polynucleotides that are complementary thereto.

The polynucleotide sequences set forth in the Sequence Listing show homology with the polynucleotide sequences set forth in Table II. A polynucleotide sequence set forth in the Sequence Listing is a cDNA sequence that encodes a polypeptide set forth in the Sequence Listing. A polynucleotide sequence encoding a polypeptide set forth in the Sequence Listing may be identical to a polypeptide encoding a sequence set forth in the Sequence Listing or it may be a sequence other than a sequence set forth in the Sequence Listing, which, as a result of the redundancy (degeneracy) of the genetic code, also encodes a polypeptide set forth in the Sequence Listing. A polypeptide of a sequence set forth in the Sequence Listingis related to other proteins of the gene families set forth in Table II, having homology and/or structural similarity with the polypeptides set forth in Table II. Preferred polypeptides and polynucleotides of the present invention are expected to have, *inter alia*, similar biological functions/properties to their homologous polypeptides and polynucleotides. Furthermore,

preferred polypeptides and polynucleotides of the present invention have at least one activity of the genes set forth in Table 1.

Polynucleotides of the present invention may be obtained using standard cloning and screening techniques from a cDNA library derived from mRNA from the tissues set forth in Table IV (see for instance, Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989)). Polynucleotides of the invention can also be obtained from natural sources such as genomic DNA libraries or can be synthesized using well known and commercially available techniques.

When polynucleotides of the present invention are used for the recombinant production of polypeptides of the present invention, the polynucleotide may include the coding sequence for the mature polypeptide, by itself, or the coding sequence for the mature polypeptide in reading frame with other coding sequences, such as those encoding a leader or secretory sequence, a pre-, or pro- or prepro- protein sequence, or other fusion peptide portions. For example, a marker sequence that facilitates purification of the fused polypeptide can be encoded. In certain preferred embodiments of this aspect of the invention, the marker sequence is a hexa-histidine peptide, as provided in the pQE vector (Qiagen, Inc.) and described in Gentz *et al.*, Proc Natl Acad Sci USA (1989) 86:821-824, or is an HA tag. A polynucleotide may also contain non-coding 5' and 3' sequences, such as transcribed, non-translated sequences, splicing and polyadenylation signals, ribosome binding sites and sequences that stabilize mRNA.

Polynucleotides that are identical, or have sufficient identity to a polynucleotide sequence set forth in the Sequence Listing, may be used as hybridization probes for cDNA and genomic DNA or as primers for a nucleic acid amplification reaction (for instance, PCR). Such probes and primers may be used to isolate full-length cDNAs and genomic clones encoding polypeptides of the present invention and to isolate cDNA and genomic clones of other genes (including genes encoding paralogs from human sources and orthologs and paralogs from species other than) that have a high sequence similarity to sequences set forth in the Sequence Listing, typically at least 95% identity. Preferred probes and primers will generally comprise at least 15 nucleotides, preferably, at least 30 nucleotides and may have at least 50, if not at least 100 nucleotides. Particularly preferred probes will have between 30 and 50 nucleotides. Particularly preferred primers will have between 20 and 25 nucleotides.

A polynucleotide encoding a polypeptide of the present invention, including homologs from species other than , may be obtained by a process comprising the steps of screening a library under stringent hybridization conditions with a labeled probe having a

sequence set forth in the Sequence Listing or a fragment thereof, preferably of at least 15 nucleotides; and isolating full-length cDNA and genomic clones containing the polynucleotide sequence set forth in the Sequence Listing. Such hybridization techniques are well known to the skilled artisan. Preferred stringent hybridization conditions include overnight incubation at 42°C in a solution comprising: 50% formamide, 5xSSC (150mM NaCl, 15mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10 % dextran sulfate, and 20 microgram/ml denatured, sheared salmon sperm DNA; followed by washing the filters in 0.1x SSC at about 65°C. Thus the present invention also includes isolated polynucleotides, preferably with a nucleotide sequence of at least 100, obtained by screening a library under stringent hybridization conditions with a labeled probe having the sequence set forth in the Sequence Listing or a fragment thereof, preferably of at least 15 nucleotides.

The skilled artisan will appreciate that, in many cases, an isolated cDNA sequence will be incomplete, in that the region coding for the polypeptide does not extend all the way through to the 5' terminus. This is a consequence of reverse transcriptase, an enzyme with inherently low "processivity" (a measure of the ability of the enzyme to remain attached to the template during the polymerisation reaction), failing to complete a DNA copy of the mRNA template during first strand cDNA synthesis.

There are several methods available and well known to those skilled in the art to obtain full-length cDNAs, or extend short cDNAs, for example those based on the method of Rapid Amplification of cDNA ends (RACE) (see, for example, Frohman et al., Proc Nat Acad Sci USA 85, 8998-9002, 1988). Recent modifications of the technique, exemplified by the Marathon (trade mark) technology (Clontech Laboratories Inc.) for example, have significantly simplified the search for longer cDNAs. In the Marathon (trade mark) technology, cDNAs have been prepared from mRNA extracted from a chosen tissue and an 'adaptor' sequence ligated onto each end. Nucleic acid amplification (PCR) is then carried out to amplify the "missing" 5' end of the cDNA using a combination of gene specific and adaptor specific oligonucleotide primers. The PCR reaction is then repeated using 'nested' primers, that is, primers designed to anneal within the amplified product (typically an adapter specific primer that anneals further 3' in the adaptor sequence and a gene specific primer that anneals further 5' in the known gene sequence). The products of this reaction can then be analyzed by DNA sequencing and a full-length cDNA constructed either by joining the product directly to the existing cDNA to give a complete sequence, or carrying out a separate full-length PCR using the new sequence information for the design of the 5' primer.

Recombinant polypeptides of the present invention may be prepared by processes well known in the art from genetically engineered host cells comprising expression systems. Accordingly, in a further aspect, the present invention relates to expression systems comprising a polynucleotide or polynucleotides of the present invention, to host cells which are genetically engineered with such expression systems and to the production of polypeptides of the invention by recombinant techniques. Cell-free translation systems can also be employed to produce such proteins using RNAs derived from the DNA constructs of the present invention.

For recombinant production, host cells can be genetically engineered to incorporate expression systems or portions thereof for polynucleotides of the present invention. Polynucleotides may be introduced into host cells by methods described in many standard laboratory manuals, such as Davis et al., Basic Methods in Molecular Biology (1986) and Sambrook *et al.*(*ibid*). Preferred methods of introducing polynucleotides into host cells include, for instance, calcium phosphate transfection, DEAE-dextran mediated transfection, transvection, micro-injection, cationic lipid-mediated transfection, electroporation, transduction, scrape loading, ballistic introduction or infection.

Representative examples of appropriate hosts include bacterial cells, such as *Streptococci*, *Staphylococci*, *E. coli*, *Streptomyces* and *Bacillus subtilis* cells; fungal cells, such as yeast cells and *Aspergillus* cells; insect cells such as *Drosophila* S2 and *Spodoptera* Sf9 cells; animal cells such as CHO, COS, HeLa, C127, 3T3, BHK, HEK 293 and Bowes melanoma cells; and plant cells.

A great variety of expression systems can be used, for instance, chromosomal, episomal and virus-derived systems, *e.g.*, vectors derived from bacterial plasmids, from bacteriophage, from transposons, from yeast episomes, from insertion elements, from yeast chromosomal elements, from viruses such as baculoviruses, papova viruses, such as SV40, vaccinia viruses, adenoviruses, fowl pox viruses, pseudorabies viruses and retroviruses, and vectors derived from combinations thereof, such as those derived from plasmid and bacteriophage genetic elements, such as cosmids and phagemids. The expression systems may contain control regions that regulate as well as engender expression. Generally, any system or vector that is able to maintain, propagate or express a polynucleotide to produce a polypeptide in a host may be used. The appropriate polynucleotide sequence may be inserted into an expression system by any of a variety of well-known and routine techniques, such as, for example, those set forth in Sambrook *et al.*, (*ibid*). Appropriate secretion signals may be incorporated into the desired polypeptide to allow secretion of the translated protein into the

lumen of the endoplasmic reticulum, the periplasmic space or the extracellular environment. These signals may be endogenous to the polypeptide or they may be heterologous signals.

If a polypeptide of the present invention is to be expressed for use in screening assays, it is generally preferred that the polypeptide be produced at the surface of the cell. In this event, the cells may be harvested prior to use in the screening assay. If the polypeptide is secreted into the medium, the medium can be recovered in order to recover and purify the polypeptide. If produced intracellularly, the cells must first be lysed before the polypeptide is recovered.

Polypeptides of the present invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography is employed for purification. Well known techniques for refolding proteins may be employed to regenerate active conformation when the polypeptide is denatured during intracellular synthesis, isolation and/or purification.

Polynucleotides of the present invention may be used as diagnostic reagents, through detecting mutations in the associated gene. Detection of a mutated form of a gene is characterized by the polynucleotides set forth in the Sequence Listing in the cDNA or genomic sequence and which is associated with a dysfunction. Will provide a diagnostic tool that can add to, or define, a diagnosis of a disease, or susceptibility to a disease, which results from under-expression, over-expression or altered spatial or temporal expression of the gene. Individuals carrying mutations in the gene may be detected at the DNA level by a variety of techniques well known in the art.

Nucleic acids for diagnosis may be obtained from a subject's cells, such as from blood, urine, saliva, tissue biopsy or autopsy material. The genomic DNA may be used directly for detection or it may be amplified enzymatically by using PCR, preferably RT-PCR, or other amplification techniques prior to analysis. RNA or cDNA may also be used in similar fashion. Deletions and insertions can be detected by a change in size of the amplified product in comparison to the normal genotype. Point mutations can be identified by hybridizing amplified DNA to labeled nucleotide sequences of the genes set forth in Table I. Perfectly matched sequences can be distinguished from mismatched duplexes by RNase digestion or by differences in melting temperatures. DNA sequence difference may also be detected by alterations in the electrophoretic mobility of DNA fragments in gels, with or without denaturing agents, or by direct DNA sequencing (see, for instance, Myers *et al.*,

Science (1985) 230:1242). Sequence changes at specific locations may also be revealed by nuclease protection assays, such as RNase and S1 protection or the chemical cleavage method (see Cotton *et al.*, Proc Natl Acad Sci USA (1985) 85: 4397-4401).

An array of oligonucleotides probes comprising polynucleotide sequences or fragments thereof of the genes set forth in Table I can be constructed to conduct efficient screening of *e.g.*, genetic mutations. Such arrays are preferably high density arrays or grids. Array technology methods are well known and have general applicability and can be used to address a variety of questions in molecular genetics including gene expression, genetic linkage, and genetic variability, see, for example, M. Chee et al., Science, 274, 610-613 (1996) and other references cited therein.

Detection of abnormally decreased or increased levels of polypeptide or mRNA expression may also be used for diagnosing or determining susceptibility of a subject to a disease of the invention. Decreased or increased expression can be measured at the RNA level using any of the methods well known in the art for the quantitation of polynucleotides, such as, for example, nucleic acid amplification, for instance PCR, RT-PCR, RNase protection, Northern blotting and other hybridization methods. Assay techniques that can be used to determine levels of a protein, such as a polypeptide of the present invention, in a sample derived from a host are well-known to those of skill in the art. Such assay methods include radio-immunoassays, competitive-binding assays, Western Blot analysis and ELISA assays.

Thus in another aspect, the present invention relates to a diagnostic kit comprising:

(a) a polynucleotide of the present invention, preferably the nucleotide sequence set forth in the Sequence Listing , or a fragment or an RNA transcript thereof;

(b) a nucleotide sequence complementary to that of (a);

(c) a polypeptide of the present invention, preferably the polypeptide set forth in the Sequence Listing or a fragment thereof; or

(d) an antibody to a polypeptide of the present invention, preferably to the polypeptide set forth in the Sequence Listing .

It will be appreciated that in any such kit, (a), (b), (c) or (d) may comprise a substantial component. Such a kit will be of use in diagnosing a disease or susceptibility to a disease, particularly diseases of the invention, amongst others.

The polynucleotide sequences of the present invention are valuable for chromosome localisation studies. The sequences set forth in the Sequence Listing are specifically targeted to, and can hybridize with, a particular location on an individual human chromosome. The mapping of relevant sequences to chromosomes according to the present invention is an important first step in correlating those sequences with gene associated disease. Once a

sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data. Such data are found in, for example, V. McKusick, Mendelian Inheritance in Man (available on-line through Johns Hopkins University Welch Medical Library). The relationship between genes and diseases that have been mapped to the same chromosomal region are then identified through linkage analysis (co-inheritance of physically adjacent genes). Precise human chromosomal localisations for a genomic sequence (gene fragment etc.) can be determined using Radiation Hybrid (RH) Mapping (Walter, M. Spillett, D., Thomas, P., Weissenbach, J., and Goodfellow, P., (1994) A method for constructing radiation hybrid maps of whole genomes, Nature Genetics 7, 22-28). A number of RH panels are available from Research Genetics (Huntsville, AL, USA) e.g. the GeneBridge4 RH panel (Hum Mol Genet 1996 Mar;5(3):339-46 A radiation hybrid map of the human genome. Gyapay G, Schmitt K, Fizames C, Jones H, Vega-Czarny N, Spillett D, Muselet D, Prud'Homme JF, Dib C, Auffray C, Morissette J, Weissenbach J, Goodfellow PN). To determine the chromosomal location of a gene using this panel, 93 PCRs are performed using primers designed from the gene of interest on RH DNAs. Each of these DNAs contains random human genomic fragments maintained in a hamster background (human / hamster hybrid cell lines). These PCRs result in 93 scores indicating the presence or absence of the PCR product of the gene of interest. These scores are compared with scores created using PCR products from genomic sequences of known location. This comparison is conducted at http://www.genome.wi.mit.edu/.

The polynucleotide sequences of the present invention are also valuable tools for tissue expression studies. Such studies allow the determination of expression patterns of polynucleotides of the present invention which may give an indication as to the expression patterns of the encoded polypeptides in tissues, by detecting the mRNAs that encode them. The techniques used are well known in the art and include in situ hydridization techniques to clones arrayed on a grid, such as cDNA microarray hybridization (Schena *et al*, Science, 270, 467-470, 1995 and Shalon *et al*, Genome Res, 6, 639-645, 1996) and nucleotide amplification techniques such as PCR. A preferred method uses the TAQMAN (Trade mark) technology available from Perkin Elmer. Results from these studies can provide an indication of the normal function of the polypeptide in the organism. In addition, comparative studies of the normal expression pattern of mRNAs with that of mRNAs encoded by an alternative form of the same gene (for example, one having an alteration in polypeptide coding potential or a regulatory mutation) can provide valuable insights into the role of the polypeptides of the present invention, or that of inappropriate expression thereof in disease. Such inappropriate expression may be of a temporal, spatial or simply quantitative nature.

A further aspect of the present invention relates to antibodies. The polypeptides of the invention or their fragments, or cells expressing them, can be used as immunogens to produce antibodies that are immunospecific for polypeptides of the present invention. The term "immunospecific" means that the antibodies have substantially greater affinity for the polypeptides of the invention than their affinity for other related polypeptides in the prior art.

Antibodies generated against polypeptides of the present invention may be obtained by administering the polypeptides or epitope-bearing fragments, or cells to an animal, preferably a non-human animal, using routine protocols. For preparation of monoclonal antibodies, any technique which provides antibodies produced by continuous cell line cultures can be used. Examples include the hybridoma technique (Kohler, G. and Milstein, C., Nature (1975) 256:495-497), the trioma technique, the human B-cell hybridoma technique (Kozbor *et al.*, Immunology Today (1983) 4:72) and the EBV-hybridoma technique (Cole *et al.*, Monoclonal Antibodies and Cancer Therapy, 77-96, Alan R. Liss, Inc., 1985).

Techniques for the production of single chain antibodies, such as those described in U.S. Patent No. 4,946,778, can also be adapted to produce single chain antibodies to polypeptides of this invention. Also, transgenic mice, or other organisms, including other mammals, may be used to express humanized antibodies.

The above-described antibodies may be employed to isolate or to identify clones expressing the polypeptide or to purify the polypeptides by affinity chromatography. Antibodies against polypeptides of the present invention may also be employed to treat diseases of the invention, amongst others.

Polypeptides and polynucleotides of the present invention may also be used as vaccines. Accordingly, in a further aspect, the present invention relates to a method for inducing an immunological response in a mammal that comprises inoculating the mammal with a polypeptide of the present invention, adequate to produce antibody and/or T cell immune response, including, for example, cytokine-producing T cells or cytotoxic T cells, to protect said animal from disease, whether that disease is already established within the individual or not. An immunological response in a mammal may also be induced by a method comprises delivering a polypeptide of the present invention *via* a vector directing expression of the polynucleotide and coding for the polypeptide *in vivo* in order to induce such an immunological response to produce antibody to protect said animal from diseases of the invention. One way of administering the vector is by accelerating it into the desired cells as a coating on particles or otherwise. Such nucleic acid vector may comprise DNA, RNA, a modified nucleic acid, or a DNA/RNA hybrid. For use a vaccine, a polypeptide or a nucleic acid vector will be normally provided as a vaccine formulation (composition). The

formulation may further comprise a suitable carrier. Since a polypeptide may be broken down in the stomach, it is preferably administered parenterally (for instance, subcutaneous, intra-muscular, intravenous, or intra-dermal injection). Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions that may contain anti-oxidants, buffers, bacteriostats and solutes that render the formulation instonic with the blood of the recipient; and aqueous and non-aqueous sterile suspensions that may include suspending agents or thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampoules and vials and may be stored in a freeze-dried condition requiring only the addition of the sterile liquid carrier immediately prior to use. The vaccine formulation may also include adjuvant systems for enhancing the immunogenicity of the formulation, such as oil-in water systems and other systems known in the art. The dosage will depend on the specific activity of the vaccine and can be readily determined by routine experimentation.

Polypeptides of the present invention have one or more biological functions that are of relevance in one or more disease states, in particular the diseases of the invention hereinbefore mentioned. It is therefore useful to identify compounds that stimulate or inhibit the function or level of the polypeptide. Accordingly, in a further aspect, the present invention provides for a method of screening compounds to identify those that stimulate or inhibit the function or level of the polypeptide. Such methods identify agonists or antagonists that may be employed for therapeutic and prophylactic purposes for such diseases of the invention as hereinbefore mentioned. Compounds may be identified from a variety of sources, for example, cells, cell-free preparations, chemical libraries, collections of chemical compounds, and natural product mixtures. Such agonists or antagonists so-identified may be natural or modified substrates, ligands, receptors, enzymes, etc., as the case may be, of the polypeptide; a structural or functional mimetic thereof (see Coligan *et al.*, Current Protocols in Immunology 1(2):Chapter 5 (1991)) or a small molecule. Such small molecules preferably have a molecular weight below 2,000 daltons, more preferably between 300 and 1,000 daltons, and most preferably between 400 and 700 daltons. It is preferred that these small molecules are organic molecules.

The screening method may simply measure the binding of a candidate compound to the polypeptide, or to cells or membranes bearing the polypeptide, or a fusion protein thereof, by means of a label directly or indirectly associated with the candidate compound. Alternatively, the screening method may involve measuring or detecting (qualitatively or quantitatively) the competitive binding of a candidate compound to the polypeptide against a labeled competitor (*e.g.* agonist or antagonist). Further, these screening methods may test

whether the candidate compound results in a signal generated by activation or inhibition of the polypeptide, using detection systems appropriate to the cells bearing the polypeptide. Inhibitors of activation are generally assayed in the presence of a known agonist and the effect on activation by the agonist by the presence of the candidate compound is observed. Further, the screening methods may simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide of the present invention, to form a mixture, measuring an activity of the genes set forth in Table I in the mixture, and comparing activity of the mixture of the genes set forth in Table 1 to a control mixture which contains no candidate compound.

Polypeptides of the present invention may be employed in conventional low capacity screening methods and also in high-throughput screening (HTS) formats. Such HTS formats include not only the well-established use of 96- and, more recently, 384-well micotiter plates but also emerging methods such as the nanowell method described by Schullek et al, Anal Biochem., 246, 20-29, (1997).

Fusion proteins, such as those made from Fc portion and polypeptide of the genes set forth in Table I, as hereinbefore described, can also be used for high-throughput screening assays to identify antagonists for the polypeptide of the present invention (see D. Bennett *et al.*, J Mol Recognition, 8:52-58 (1995); and K. Johanson *et al.*, J Biol Chem, 270(16):9459-9471 (1995)).

The polynucleotides, polypeptides and antibodies to the polypeptide of the present invention may also be used to configure screening methods for detecting the effect of added compounds on the production of mRNA and polypeptide in cells. For example, an ELISA assay may be constructed for measuring secreted or cell associated levels of polypeptide using monoclonal and polyclonal antibodies by standard methods known in the art. This can be used to discover agents that may inhibit or enhance the production of polypeptide (also called antagonist or agonist, respectively) from suitably manipulated cells or tissues.

A polypeptide of the present invention may be used to identify membrane bound or soluble receptors, if any, through standard receptor binding techniques known in the art. These include, but are not limited to, ligand binding and crosslinking assays in which the polypeptide is labeled with a radioactive isotope (for instance, ^{125}I), chemically modified (for instance, biotinylated), or fused to a peptide sequence suitable for detection or purification, and incubated with a source of the putative receptor (cells, cell membranes, cell supernatants, tissue extracts, bodily fluids). Other methods include biophysical techniques such as surface plasmon resonance and spectroscopy. These screening methods may also be used to identify agonists and antagonists of the polypeptide that compete with the binding of the polypeptide

to its receptors, if any. Standard methods for conducting such assays are well understood in the art.

Examples of antagonists of polypeptides of the present invention include antibodies or, in some cases, oligonucleotides or proteins that are closely related to the ligands, substrates, receptors, enzymes, etc., as the case may be, of the polypeptide, *e.g.*, a fragment of the ligands, substrates, receptors, enzymes, etc.; or a small molecule that bind to the polypeptide of the present invention but do not elicit a response, so that the activity of the polypeptide is prevented.

Screening methods may also involve the use of transgenic technology and the genes set forth in Table I. The art of constructing transgenic animals is well established. For example, the genes set forth in Table I may be introduced through microinjection into the male pronucleus of fertilized oocytes, retroviral transfer into pre- or post-implantation embryos, or injection of genetically modified, such as by electroporation, embryonic stem cells into host blastocysts. Particularly useful transgenic animals are so-called "knock-in" animals in which an animal gene is replaced by the human equivalent within the genome of that animal. Knock-in transgenic animals are useful in the drug discovery process, for target validation, where the compound is specific for the human target. Other useful transgenic animals are so-called "knock-out" animals in which the expression of the animal ortholog of a polypeptide of the present invention and encoded by an endogenous DNA sequence in a cell is partially or completely annulled. The gene knock-out may be targeted to specific cells or tissues, may occur only in certain cells or tissues as a consequence of the limitations of the technology, or may occur in all, or substantially all, cells in the animal. Transgenic animal technology also offers a whole animal expression-cloning system in which introduced genes are expressed to give large amounts of polypeptides of the present invention

Screening kits for use in the above described methods form a further aspect of the present invention. Such screening kits comprise:

(a) a polypeptide of the present invention;

(b) a recombinant cell expressing a polypeptide of the present invention;

(c) a cell membrane expressing a polypeptide of the present invention; or

(d) an antibody to a polypeptide of the present invention;

which polypeptide is preferably that set forth in the Sequence Listing.

It will be appreciated that in any such kit, (a), (b), (c) or (d) may comprise a substantial component.

Glossary

The following definitions are provided to facilitate understanding of certain terms used frequently hereinbefore.

"Antibodies" as used herein includes polyclonal and monoclonal antibodies, chimeric, single chain, and humanized antibodies, as well as Fab fragments, including the products of an Fab or other immunoglobulin expression library.

"Isolated" means altered "by the hand of man" from its natural state, *i.e.*, if it occurs in nature, it has been changed or removed from its original environment, or both. For example, a polynucleotide or a polypeptide naturally present in a living organism is not "isolated," but the same polynucleotide or polypeptide separated from the coexisting materials of its natural state is "isolated", as the term is employed herein. Moreover, a polynucleotide or polypeptide that is introduced into an organism by transformation, genetic manipulation or by any other recombinant method is "isolated" even if it is still present in said organism, which organism may be living or non-living.

"Secreted protein activity or secreted polypeptide activity" or "biological activity of the secreted protein or secreted polypeptide" refers to the metabolic or physiologic function of said secreted protein including similar activities or improved activities or these activities with decreased undesirable side-effects. Also included are antigenic and immunogenic activities of said secreted protein.

"Secreted protein gene" refers to a polynucleotide comprising any of the attached nucleotide sequences or allelic variants thereof and/or their complements.

"Polynucleotide" generally refers to any polyribonucleotide (RNA) or polydeoxribonucleotide (DNA), which may be unmodified or modified RNA or DNA. "Polynucleotides" include, without limitation, single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, "polynucleotide" refers to triple-stranded regions comprising RNA or DNA or both RNA and DNA. The term "polynucleotide" also includes DNAs or RNAs containing one or more modified bases and DNAs or RNAs with backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications may be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically or metabolically modified forms of polynucleotides as typically found in nature, as well as the chemical forms of DNA and RNA characteristic of viruses and cells. "Polynucleotide" also embraces relatively short polynucleotides, often referred to as oligonucleotides.

"Polypeptide" refers to any polypeptide comprising two or more amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres. "Polypeptide" refers to both short chains, commonly referred to as peptides, oligopeptides or oligomers, and to longer chains, generally referred to as proteins. Polypeptides may contain amino acids other than the 20 gene-encoded amino acids. "Polypeptides" include amino acid sequences modified either by natural processes, such as post-translational processing, or by chemical modification techniques that are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications may occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present to the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched and branched cyclic polypeptides may result from post-translation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, biotinylation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cystine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination (see, for instance, Proteins - Structure and Molecular Properties, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York, 1993; Wold, F., Post-translational Protein Modifications: Perspectives and Prospects, 1-12, in Post-translational Covalent Modification of Proteins, B. C. Johnson, Ed., Academic Press, New York, 1983; Seifter *et al.*, "Analysis for protein modifications and nonprotein cofactors", Meth Enzymol, 182, 626-646, 1990, and Rattan *et al.*, "Protein Synthesis: Post-translational Modifications and Aging", Ann NY Acad Sci, 663, 48-62, 1992).

"Fragment" of a polypeptide sequence refers to a polypeptide sequence that is shorter than the reference sequence but that retains essentially the same biological function or activity as the reference polypeptide. "Fragment" of a polynucleotide sequence refers to a

polynucleotide sequence that is shorter than the reference sequence set forth in the Sequence Listing.

"Variant" refers to a polynucleotide or polypeptide that differs from a reference polynucleotide or polypeptide, but retains the essential properties thereof. A typical variant of a polynucleotide differs in nucleotide sequence from the reference polynucleotide. Changes in the nucleotide sequence of the variant may or may not alter the amino acid sequence of a polypeptide encoded by the reference polynucleotide. Nucleotide changes may result in amino acid substitutions, additions, deletions, fusions and truncations in the polypeptide encoded by the reference sequence, as discussed below. A typical variant of a polypeptide differs in amino acid sequence from the reference polypeptide. Generally, alterations are limited so that the sequences of the reference polypeptide and the variant are closely similar overall and, in many regions, identical. A variant and reference polypeptide may differ in amino acid sequence by one or more substitutions, insertions, deletions in any combination. A substituted or inserted amino acid residue may or may not be one encoded by the genetic code. Typical conservative substitutions include Gly, Ala; Val, Ile, Leu; Asp, Glu; Asn, Gln; Ser, Thr; Lys, Arg; and Phe and Tyr. A variant of a polynucleotide or polypeptide may be naturally occurring such as an allele, or it may be a variant that is not known to occur naturally. Non-naturally occurring variants of polynucleotides and polypeptides may be made by mutagenesis techniques or by direct synthesis. Also included as variants are polypeptides having one or more post-translational modifications, for instance glycosylation, phosphorylation, methylation, ADP ribosylation and the like. Embodiments include methylation of the N-terminal amino acid, phosphorylations of serines and threonines and modification of C-terminal glycines.

"Allele" refers to one of two or more alternative forms of a gene occurring at a given locus in the genome.

"Polymorphism" refers to a variation in nucleotide sequence (and encoded polypeptide sequence, if relevant) at a given position in the genome within a population.

"Single Nucleotide Polymorphism" (SNP) refers to the occurrence of nucleotide variability at a single nucleotide position in the genome, within a population. An SNP may occur within a gene or within intergenic regions of the genome. SNPs can be assayed using Allele Specific Amplification (ASA). For the process at least 3 primers are required. A common primer is used in reverse complement to the polymorphism being assayed. This common primer can be between 50 and 1500 bps from the polymorphic base. The other two (or more) primers are identical to each other except that the final 3' base wobbles to match one of the two (or more) alleles that make up the polymorphism. Two (or more) PCR

reactions are then conducted on sample DNA, each using the common primer and one of the Allele Specific Primers.

"Splice Variant" as used herein refers to cDNA molecules produced from RNA molecules initially transcribed from the same genomic DNA sequence but which have undergone alternative RNA splicing. Alternative RNA splicing occurs when a primary RNA transcript undergoes splicing, generally for the removal of introns, which results in the production of more than one mRNA molecule each of that may encode different amino acid sequences. The term splice variant also refers to the proteins encoded by the above cDNA molecules.

"Identity" reflects a relationship between two or more polypeptide sequences or two or more polynucleotide sequences, determined by comparing the sequences. In general, identity refers to an exact nucleotide to nucleotide or amino acid to amino acid correspondence of the two polynucleotide or two polypeptide sequences, respectively, over the length of the sequences being compared.

"% Identity" - For sequences where there is not an exact correspondence, a "% identity" may be determined. In general, the two sequences to be compared are aligned to give a maximum correlation between the sequences. This may include inserting "gaps" in either one or both sequences, to enhance the degree of alignment. A % identity may be determined over the whole length of each of the sequences being compared (so-called global alignment), that is particularly suitable for sequences of the same or very similar length, or over shorter, defined lengths (so-called local alignment), that is more suitable for sequences of unequal length.

"Similarity" is a further, more sophisticated measure of the relationship between two polypeptide sequences. In general, "similarity" means a comparison between the amino acids of two polypeptide chains, on a residue by residue basis, taking into account not only exact correspondences between a between pairs of residues, one from each of the sequences being compared (as for identity) but also, where there is not an exact correspondence, whether, on an evolutionary basis, one residue is a likely substitute for the other. This likelihood has an associated "score" from which the "% similarity" of the two sequences can then be determined.

Methods for comparing the identity and similarity of two or more sequences are well known in the art. Thus for instance, programs available in the Wisconsin Sequence Analysis Package, version 9.1 (Devereux J et al, Nucleic Acids Res, 12, 387-395, 1984, available from Genetics Computer Group, Madison, Wisconsin, USA), for example the programs BESTFIT and GAP, may be used to determine the % identity between two polynucleotides and the %

identity and the % similarity between two polypeptide sequences. BESTFIT uses the "local homology" algorithm of Smith and Waterman (J Mol Biol, 147,195-197, 1981, Advances in Applied Mathematics, 2, 482-489, 1981) and finds the best single region of similarity between two sequences. BESTFIT is more suited to comparing two polynucleotide or two polypeptide sequences that are dissimilar in length, the program assuming that the shorter sequence represents a portion of the longer. In comparison, GAP aligns two sequences, finding a "maximum similarity", according to the algorithm of Neddleman and Wunsch (J Mol Biol, 48, 443-453, 1970). GAP is more suited to comparing sequences that are approximately the same length and an alignment is expected over the entire length. Preferably, the parameters "Gap Weight" and "Length Weight" used in each program are 50 and 3, for polynucleotide sequences and 12 and 4 for polypeptide sequences, respectively. Preferably, % identities and similarities are determined when the two sequences being compared are optimally aligned.

Other programs for determining identity and/or similarity between sequences are also known in the art, for instance the BLAST family of programs (Altschul S F et al, J Mol Biol, 215, 403-410, 1990, Altschul S F et al, Nucleic Acids Res., 25:389-3402, 1997, available from the National Center for Biotechnology Information (NCBI), Bethesda, Maryland, USA and accessible through the home page of the NCBI at www.ncbi.nlm.nih.gov) and FASTA (Pearson W R, Methods in Enzymology, 183, 63-99, 1990; Pearson W R and Lipman D J, Proc Nat Acad Sci USA, 85, 2444-2448,1988, available as part of the Wisconsin Sequence Analysis Package).

Preferably, the BLOSUM62 amino acid substitution matrix (Henikoff S and Henikoff J G, Proc. Nat. Acad Sci. USA, 89, 10915-10919, 1992) is used in polypeptide sequence comparisons including where nucleotide sequences are first translated into amino acid sequences before comparison.

Preferably, the program BESTFIT is used to determine the % identity of a query polynucleotide or a polypeptide sequence with respect to a reference polynucleotide or a polypeptide sequence, the query and the reference sequence being optimally aligned and the parameters of the program set at the default value, as hereinbefore described.

"Identity Index" is a measure of sequence relatedness which may be used to compare a candidate sequence (polynucleotide or polypeptide) and a reference sequence. Thus, for instance, a candidate polynucleotide sequence having, for example, an Identity Index of 0.95 compared to a reference polynucleotide sequence is identical to the reference sequence except that the candidate polynucleotide sequence may include on average up to five differences per each 100 nucleotides of the reference sequence. Such differences are selected from the group

consisting of at least one nucleotide deletion, substitution, including transition and transversion, or insertion. These differences may occur at the 5' or 3' terminal positions of the reference polynucleotide sequence or anywhere between these terminal positions, interspersed either individually among the nucleotides in the reference sequence or in one or more contiguous groups within the reference sequence. In other words, to obtain a polynucleotide sequence having an Identity Index of 0.95 compared to a reference polynucleotide sequence, an average of up to 5 in every 100 of the nucleotides of the in the reference sequence may be deleted, substituted or inserted, or any combination thereof, as hereinbefore described. The same applies *mutatis mutandis* for other values of the Identity Index, for instance 0.96, 0.97, 0.98 and 0.99.

Similarly, for a polypeptide, a candidate polypeptide sequence having, for example, an Identity Index of 0.95 compared to a reference polypeptide sequence is identical to the reference sequence except that the polypeptide sequence may include an average of up to five differences per each 100 amino acids of the reference sequence. Such differences are selected from the group consisting of at least one amino acid deletion, substitution, including conservative and non-conservative substitution, or insertion. These differences may occur at the amino- or carboxy-terminal positions of the reference polypeptide sequence or anywhere between these terminal positions, interspersed either individually among the amino acids in the reference sequence or in one or more contiguous groups within the reference sequence. In other words, to obtain a polypeptide sequence having an Identity Index of 0.95 compared to a reference polypeptide sequence, an average of up to 5 in every 100 of the amino acids in the reference sequence may be deleted, substituted or inserted, or any combination thereof, as hereinbefore described. The same applies *mutatis mutandis* for other values of the Identity Index, for instance 0.96, 0.97, 0.98 and 0.99.

The relationship between the number of nucleotide or amino acid differences and the Identity Index may be expressed in the following equation:

$$n_a \leq x_a - (x_a \bullet I),$$

in which:

n_a is the number of nucleotide or amino acid differences,

x_a is the total number of nucleotides or amino acids in a sequence set forth in the Sequence Listing,

I is the Identity Index,

• is the symbol for the multiplication operator, and

in which any non-integer product of x_a and l is rounded down to the nearest integer prior to subtracting it from x_a.

"Homolog" is a generic term used in the art to indicate a polynucleotide or polypeptide sequence possessing a high degree of sequence relatedness to a reference sequence. Such relatedness may be quantified by determining the degree of identity and/or similarity between the two sequences as hereinbefore defined. Falling within this generic term are the terms "ortholog", and "paralog". "Ortholog" refers to a polynucleotide or polypeptide that is the functional equivalent of the polynucleotide or polypeptide in another species. "Paralog" refers to a polynucleotideor polypeptide that within the same species which is functionally similar.

"Fusion protein" refers to a protein encoded by two, often unrelated, fused genes or fragments thereof. In one example, EP-A-0 464 533-A discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, employing an immunoglobulin Fc region as a part of a fusion protein is advantageous for use in therapy and diagnosis resulting in, for example, improved pharmacokinetic properties [see, *e.g.*, EP-A 0232 262]. On the other hand, for some uses it would be desirable to be able to delete the Fc part after the fusion protein has been expressed, detected and purified.

All publications and references, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference in their entirety as if each individual publication or reference were specifically and individually indicated to be incorporated by reference herein as being fully set forth. Any patent application to which this application claims priority is also incorporated by reference herein in its entirety in the manner described above for publications and references.

Table I.

Gene Name	GSK Gene ID	Nucleic Acid SEQ ID NO's	Corresponding Protein SEQ ID NO's
sbg101452SLITa	101452	SEQ ID NO:1	SEQ ID NO:27
sbg29046CYSa	29046a	SEQ ID NO:2	SEQ ID NO:28
sbg29046CYSb	29046b	SEQ ID NO:3 SEQ ID NO:4	SEQ ID NO:29 SEQ ID NO:30
sbg37149SLITb	37149	SEQ ID NO:5	SEQ ID NO:31
sbg36267SLIta	36267	SEQ ID NO:6	SEQ ID NO:32
sbg35579MELAa	35579	SEQ ID NO:7 SEQ ID NO:8	SEQ ID NO:33 SEQ ID NO:34
SBh69447. Triglyceride Lipase	69447	SEQ ID NO:9	SEQ ID NO:35
SBh86614.Tryp1	86614	SEQ ID NO:10 SEQ ID NO:11	SEQ ID NO:36 SEQ ID NO:37
sbg106886DELTAa	106886	SEQ ID NO:12	SEQ ID NO:38
sbg35779THYa	35779	SEQ ID NO:13	SEQ ID NO:39
sbg15130INHa	15130	SEQ ID NO:14 SEQ ID NO:15	SEQ ID NO:40 SEQ ID NO:41
SBh26548.homebox	26548	SEQ ID NO:16	SEQ ID NO:42
sbg26991CERUa	26991	SEQ ID NO:17	SEQ ID NO:43
sbg35851PEROa	35851	SEQ ID NO:18 SEQ ID NO:19	SEQ ID NO:44 SEQ ID NO:45
sbg36274SLITa	36274	SEQ ID NO:20	SEQ ID NO:46
sbg34575SLITa	34575	SEQ ID NO:21	SEQ ID NO:47
SBh71706.NIAP	71706	SEQ ID NO:22 SEQ ID NO:23	SEQ ID NO:48 SEQ ID NO:49
SBh77492.Breast Specific BS200	77492	SEQ ID NO:24 SEQ ID NO:25	SEQ ID NO:50 SEQ ID NO:51
sbg115305LRRa	115305	SEQ ID NO:26	SEQ ID NO:52

Table II

Gene Name	Gene Family	Closest Polynuclotide by homology	Closest Polypeptide by homology	Cell Localization (by homology)
sbg101452SLITa	Slit-like membrane glycoprotein	GB:AL138498 Submitted (07-DEC-2000) by Genoscope - Centre National de Sequencage : BP 191 91006 EVRY cedex - FRANCE	KIAA1246 protein,gi:6330833 Submitted (04-OCT-1999) by Osamu Ohara, Kazusa DNA Research Institute, Laboratory of DNA Technology; 1532-3 Yana, Kisarazu, Chiba 292-0812, Japan	Membrane-bound
sbg29046CYSa	Cystatin	GB:AL121894 Submitted on Feb 18,2000 by Sanger Centre, Hinxton, Cambridgeshire, CB10 1SA, UK	Human cystatin family member gi :9944240 Submitted (25-OCT-2000) Sanger Centre, Hinxton, Cambridgeshire, CB10 1SA, UK.	Secreted
sbg29046CYSb	Cystatin	GB:AL121894 Submitted on Feb 18,2000 by Sanger Centre, Hinxton, Cambridgeshire, CB10 1SA, UK	Novel human cystatin-related protcin geneseqp:Y53771 (KARO-) KAROLINSKA INNOVATIONS AB WO9958565-A1, 18-NOV-99	Secreted
sbg37149SLITb	Slit-like membrane glycoprotein	GB:Z94160 Submitted on Dec8, 1999, Sanger Centre, Hinxton, Cambridgeshire, CB10 1SA, UK.	Human putative leucine rich protein gi:3191975 Submitted (08-DEC-1999) Sanger Centre, Hinxton, Cambridgeshire, CB10 1SA, UK.	Membrane-bound
sbg36267SLIta	Slit 3-like membrane glycoprotein	GB:AL080239 Submitted on Jan10, 2000, by Sanger Centre, Hinxton, Cambridgeshire, CB10 1SA, UK.	Human KIAA0918 protein, gi :4240325 Nagase,T., Ishikawa,K., Suyama,M., Kikuno,R., Hirosawa,M., Miyajima,N., Tanaka,A., Kotani,H., Nomura,N. and Ohara,O. DNA Res. 5 (6), 355-364 (1998)	Membrane-bound
sbg35579MELAa	Brain-specific transmembrane glycoprotein	GB:AC018477 Submitted (12-DEC-1999) by Human Genome Sequencing Center, Department of Molecular and Human Genetics, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA	Human KIAA1484 protein, gi: 7959229 Nagase,T., Kikuno,R., Ishikawa,K., Hirosawa,M. and Ohara,O. DNA Res. 7 (2), 143-150 (2000).	Membrane-bound
SBh69447. Triglyceride Lipase	Triglyceride lipase	GB:AC011277 Submitted (05-OCT-1999) by Whitehead Institute/MIT Center for Genome Research, 320 Charles Street, Cambridge, MA 02141, USA	Human gastric lipase, gi:4758676 Bodmer,M.W., Angal,S., Yarranton,G.T., Harris,T.J., Lyons,A., King,D.J., Pieroni,G., Riviere,C., Verger,R. and Lowe,P.A. Biochim. Biophys. Acta 909 (3), 237-244 (1987)	Secreted

Table II Cont

Gene Name	Gene Family	Closest Polynuclotide by homology	Closest Polypeptide by homology	Cell Localization (by homology)
SBh86614.Trypl	Serine protease	JGI:RPCI-11± 388M20 Found at Joint Genome Institute	Human PRO351 protein, geneseqp:Y41704 GENENTECH INC WO9946281-A2, 16-SEP-99	Secreted
sbg106886DELTA a	DELTAa	GB:AC021391 Submitted on JAN 16, 2000, Whitehead Institute/MIT Center for Genome Research, 320 Charles Street, Cambridge, MA 02141, USA	Rat preadipocyte factor , gi: 802014 Carlsson,C., Tornehave,D., Lindberg,K., Galante,P., Billestrup,N., Michelsen,B., Larsson,L.I. and Nielsen,J.H. Endocrinology 138 (9), 3940-3948 (1997)	Secreted
sbg35779THYa	Thyroxine binding globulin	GB:AL132990 Submitted (27-JAN-2000) by Genoscope – Centre National de Sequencage :BP 191 91006 EVRY cedex	Human PRO1337 GENENTECH INC WO200012708-A2, 09-MAR-00	Secreted
sbg15130INHa	Leukocyte protease inhibitor	SC:Z93016 Submitted (31-JUL-2000) Sanger Centre, Hinxton, Cambridgeshire, CB10 1SA, UK.	Human serine protease inhibitor, geneseqp:Y28645 Human Genome Sci Inc WO199940183-A1, 12-AUG-99	Secreted
SBh26548.homebo x	LBX, HOX, DLX	GB:AC005041 Sulston,J.E. and Waterston,R. Genome Res. 8 (11), 1097-1108 (1998)	Mouse lady bird-like homeobox 2 homolog, gi: 6754512 Chen,F., Liu,K.C. and Epstein,J.A. Mech. Dev. (1999).	Nucleus
sbg26991CERUa	Ceruloplasm in precursor	GB:AC010909 Submitted (26-SEP-1999) by Whitehead Institute/MIT Center for Genome Research, 320 Charles Street, Cambridge, MA 02141, USA	Human ceruloplasmin, gi: 1070458 Takahashi,N., Ortel,T.L. and Putnam,F.W. Proc. Natl. Acad. Sci. U.S.A. 81 (2), 390-394 (1984).	Secreted
sbg35851PEROa	Slit-like membrane glycoprotein	GB:AF038458 Submitted (12-DEC-1997) Human Genome Center, Lawrence Livermore National Laboratory, 7000 East Ave., Livermore, CA 94551, USA	Human KIAA1246 protein,gi:6330833 Submitted (04-OCT-1999) by Osamu Ohara, Kazusa DNA Research Institute, Laboratory of DNA Technology; 1532-3 Yana, Kisarazu, Chiba 292-0812, Japan	Membrane-bound
sbg36274SLITa	Slit-like membrane glycoprotein	GB:AL109653 Submitted (22-NOV-1999) Sanger Centre, Hinxton, Cambridgeshire, CB10 1SA, UK.	Human novel protein, gi: 11877257 Submitted (20-JAN-2000) Sanger Centre, Hinxton, Cambridgeshire, CB10 1SA	Membrane-bound

Table II Cont

Gene Name	Gene Family	Closest Polynuclotide by homology	Closest Polypeptide by homology	Cell Localization (by homology)
sbg34575SLITa	Slit-like membrane glycoprotein	GB:AC005343 Submitted (31-JUL-1998) by Molecular and Human Genetics, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA.	pineal gland specific gene-1 protein, geneseqp: W09405 Huaman Genome Sci Inc WO9639158-A1, 12-DEC-96	Membrane-bound
SBh71706.NIAP	Apoptosis inhibitory protein	GB:AL121653 Submission (29-FEB-2000) by Genoscope.	Human hypothetical protein, weakly similar to mouse neuronal apoptosis inhibitory protein 2, gi:9367840 Submitted (15-JUL-2000) by Dept. Genetica Molecular, Institut de Recerca Oncologica (IRO), Hospital Duran i Reynals, Av. Gran Via s/n Km 2,7 L'Hospitalet de Llobregat, 08907 Barcelona, Catalunya, SPAIN.	Cytosolic
SBh77492.Breast Specific BS200	EGF-related protein	SC:Z82214,GB:Z99756 Submitted (08-DEC-1999) by Sanger Centre, Hinxton, Cambridgeshire, CB10 1SA, UK.	Mouse EGF-related protein SCUBE1, gi: 10998440 Submitted (08-JUN-2000) Mammalian Genetics Unit, MRC Harwell, Chilton, Didcot, Oxon OX11 0RD, United Kingdom.	Secreted
sbg115305LRRa	Lucine-rich repeat (LRR)	GB:AC023484 Submitted (14-FEB-2000) Human Genomic Center, Institute of Genetics, Chinese Academy of Sciences, Datun Road, Beijing, Beijing 100101, P.R.China	Muse leucine rich repeat protein 1, gi:678724 Taguchi A, Wanaka A, Mori T, Matsumoto K, Imai Y, Tagaki T, Tohyama M, 1996, Brain Res Mol Brain Res;35:31-4.	Membrane-bound

Table III.

Gene Name	Uses	Associated Diseases
sbg101452SLITa	An embodiment of the invention is the use of sbg101452SLITa, a member of the slit protein family, for diagnosis and treatment of nervous and muscular diseases. This is because other members of the slit protein family may be necessary for CNS development. In addition, sbg101452SLITa shows homology to leucine-rich repeat proteins, which demonstrates siginificant functions in neural development. It is thus possible that similar molecules play a crucial role in the morphogenesis of the mammalian nervous system (Taniguchi H, Tohyama M, Takagi T. Brain Res Mol Brain Res 1996 Feb;36(1):45-52).	Gastrointestinal ulceration, Zollinger-Ellison syndrome, congenital microvillus atrophy, skin diseases
sbg29046CYSa	An embodiment of the invention is the use of sbg29046CYSa to inhibit tumor formation and metastasis and may also be involved in natural tissue remodeling events such as bone resorption and embryo implantation. Close Homologs of sbg29046CYSa are cysteine protease inhibitors known as cystatins. Cystatins and their target proteases have been associated with tumor formation and metastasis, but also are involved in natural tissue remodeling events such as bone resorption and embryo implantation (Tohonen V., Osterlund C., and Nordqvist K., 1998 Proc Natl Acad Sci U S A 95(24):14208-13). Cystatin is a natural and specific inhibitor of the cysteine proteases generating in cancer invasion. The level of cystatin determination in serum and tissue extracts can be the clinical diagnostic and prognostic parameters in human cancers (Kos J., Stabuc B., Cimerman N., and Brunner N., 1998. Clin Chem 44(12):2556-7).	Cancer, infection, autoimmune disorder, hematopoietic disorder, wound healing, inflammation metastasis, amyloid angiopathies, and progressive myoclonus epilepsy
sbg29046CYSb	An embodiment of the invention is the use of sbg29046CYSb to inhibit tumor formation and metastasis and may also be involved in natural tissue remodeling events such as bone resorption and embryo implantation. Close homologs of sbg29046CYSa are cysteine protease inhibitors known as cystatins. Cystatins and their target proteases have been associated with tumor formation and metastasis, but also are involved in natural tissue remodeling events such as bone resorption and embryo implantation (Tohonen V., Osterlund C., and Nordqvist K., 1998 Proc Natl Acad Sci U S A 95(24):14208-13). Cystatin is a natural and specific inhibitor of the cysteine proteases generating in cancer invasion. The level of cystatin determination in serum and tissue extracts can be the clinical diagnostic and prognostic parameters in human cancers (Kos J., Stabuc B., Cimerman N., and Brunner N., 1998. Clin Chem 44(12):2556-7).	Cancer, infection, autoimmune disorder, hematopoietic disorder, wound healing, inflammation metastasis, amyloid angiopathies, and progressive myoclonus epilepsy
sbg37149SLITb	An embodiment of the invention is the use of sbg37149SLITb, a member of human slit-like proteins, which may be necessary for CNS development, and therefore can be useful for diagnosis and treatment of nervous and muscular diseases. In addition, sbg371495SLITb shows similarity to leucine-rich repeat proteins, and may also demonstrate significant functions in neural development. It has been shown that expression of slit genes is associated with neuronal migration in the developing forebrain (Hu H, Neuron 703-11,1999). It is thus possible that sbg37149SLITb plays a crucial role in the morphogenesis of the mammalian nervous system (Taniguchi H, Tohyama M, Takagi T. Brain Res Mol Brain Res 1996 Feb;36(1):45-52)	Cancer, infection,autoimmune disorder, hematopoietic disorder, wound healing, inflammation, and diseases in spinal cord, thyroid gland, ovary, prostate, renal gland, small intestine, heart, trachea, thymus, lymph node, and muscular system

Table III Cont

Gene Name	Uses	Associated Diseases
sbg36267SLITa	An embodiment of the invention is the use of sbg36267SLITa to treat gastrointestinal ulceration as well as prevention and treatment of diseases in spinal cord, thyroid gland, ovary, prostate, renal gland, small intestine, heart, trachea, thymus, lymph node, muscular system and colon. sbg36267SLITa is exploitable in similar ways to a close homolog human KIAA0918 protein, which is functionally related to cell signaling/communication, cell structure/motility and nucleic acid management. A close homolog of sbg36267SLITa is PRO266 and human slit 3 mature protein.	Gastrointestinal ulceration, diseases in spinal cord, thyroid gland, ovary, prostate, renal gland, small intestine, heart, trachea, thymus, lymph node, muscular system and colon
sbg35579MELAa	An embodiment of the invention is the use of sbg35579MELAa The closest homologue to this novel protein is human KIAA1484 protein which is derived from brain-specific cDNA library and functionally related to cell signaling/communication, cell structure/motility and nucleic acid management. Other close homologs to sbg35579MELAa are human KIAA1246, also derived from brain-specific cDNA library andhuman brain-specific transmembrane glycoprotein B09968. B09968 has a typical PDZ protein binding motif and functions as a cellular signal transducer, useful in developing drugs for treating nervous diseases	Gastrointestinal ulceration, diseases in spinal cord, thyroid gland, ovary, prostate, renal gland, small intestine, heart, trachea, thymus, lymph node, muscular system and colon.
SBh69447. Triglyceride Lipase	An embodiment of the invention is the use of SBh69447.Triglyceride Lipase, a member of gastric lipases, for oral administration to treat lipase deficiency in cystic fibrosis and pancreatitis. Some gastric lipases are also useful therapeutically for absorption of ingested fat in patients with mucoviscidioin of fat and defective transesterication (WO8601532-A).	Cancer, infection,autoimmune disorder, hematopoietic disorder, wound healing, inflammation, gastric lipase deficiency, cystic fibrosis,Pancreatitis, altered absorption of fat, gastrointestinal disorders, defective biocatalysis, mucoviscidosis, poor enymatic bioconversion of fat. cystic fibrosis, pncreatititis diseases
SBh86614.Tryp1	An embodiment of the invention is the use of SBh86614.Tryp1, a member of the mast cell protease/ tryptase family, for treatment of undesirable clot formation such as myocardial infraction, during angioplasty and all surgical procedures that require decreased blood clot formation and may also be involved in tumor growth and fertility. Other homologs of the mast cell protease/ tryptase family have been identified in WO9836054-A1 and WO9824886-A1.	Cancer, infection,autoimmune disorder, hematopoietic disorder, wound healing disorder, inflammation, blood coagulation disorders, cancers and cellular adhesion disorders, deep vein thrombosis, myocardial infraction
sbg106886 DELTAa	An embodiment of the invention is the use of sbg106886DELTAa in cellular interactions and fetal development. Close homologs of sbg106886DELTAa are involved in cell-to-cell communications in mammalian embryos through the Notch signaling pathway, and therefore may have a role in cellular interactions (Artavanis-Tsakonas et al., 1995, Science 268: 225-232). It has been shown that mouse Delta1 protein is essential for normal somitogenesis and neuronal differentiation, and Delta1 expression can be detected during organogenesis and fetal development (Beckers J., Clark A., Wunsch K., Hrabe De Angelis M., Gossler A. 1999, Mech Dev 84:165-8).	Cancer, infection, autoimmune disorder, hematopoietic disorder, wound healing, inflammation

Table III Cont.

Gene Name	Uses	Associated Diseases
sbg35779THYa	An embodiment of the invention is the use of sbg35779THYa, a secreted protein, in the diagnosis and also in the treatment of thyroid and liver diseases, treatment of septic shock, pancreatitis, coagulation disorders, and microbial diseases. Close homologs of sbg35779THYa are Mutant Human alpha-1-antichymotrypsin with Arg(358) and Alpha-1-antichymotrypsin (Leu358Arg).	Thyroid and liver diseases, septic shock, pancreatitis, coagulation disorders, microbial diseases
sbg15130INHa	An embodiment of the invention is the use of sbg15130INHa, a secreted protein, in developing products for treating e.g. immune disorders, cancers, inflammation, transplant rejection or infections. A close homolog of sbg15130INHa is mouse and rat secretory leukocyte protease inhibitors (SLIPI). Transfection of macrophages with SLPI have been shown to suppress LPS-induced activation of NF-kappa B and production of nitric oxide and TNF alpha (Jin,F.Y., Nathan,C., Radzioch,D. and Ding,A. Cell 88 (3), 417-426 (1997).	Immune disorders, cancers, inflammation, transplant rejection or infections, disorders in fetal development
SBh26548.home-box	An embodiment of the invention is the use of SBh26548 homebox to enhance bone thickness and increase bone density at the site of application or may affect developmental conditions if expressed in the thymus or T cells. Close homologs of SBh26548 homebox are members of HOX and DLX (US5850002-A and WO9943784-A2).	Autoimmune disorder, hematopoietic disorder, wound healing disorder, cancer, inflammation, viral and bacterial infection, autosomal dominant disorder, bone defects, osteoperosis, trauma, peridontal defects
sbg26991CERUa	An embodiment of the invention is the use of sbg26991CERUa to reduce the loss of essential ferroxidases. Copper is an essential trace metal which plays a fundamental role in the biochemistry of the human nervous system. Close homologs of sbg26991CERUa are Ceruloplasmins. Ceruloplasmins are plasma metalloproteins that contains 95% of the copper found in human plasma and inherited loss of this essential ferroxidase is associated with progressive neurodegeneration of the retina and basal ganglia (Waggoner DJ, Bartnikas TB, Gitlin JD, 1999 Neurobiol Dis 6(4):221-30). Ceruloplasmin deficiency leads to iron accumulation and causes damage to a variety of tissues and organs. Serum ceruloplamin determination can be part of diagnostic procedures of Wilson's disease, an inherited copper storage disease.	Cancer, infection, autoimmune disorder, hematopoietic disorder, wound healing disorder, inflammation, and progressive neurodegeneration of the retina and basal ganglia
sbg35851PEROa	An embodiment of the invention is the use of sbg35851PEROa, a member of the slit protein family, for diagnosis and treatment of nervous and muscular diseases. In addition, sbg35851PEROa shows homologyto leucine-rich repeat proteins, which demonstrates siginificant functions in neural development. It is thus possible that similar molecules play a crucial role in the morphogenesis of the mammalian nervous system (Taniguchi H, Tohyama M, Takagi T. Brain Res Mol Brain Res 1996 Feb;36(1):45-52).	Cancer, Gastrointestinal ulceration, Zollinger-Ellison syndrome, congenital microvillus atrophy, skin diseases, diseases associated with nervous system.
sbg36274SLITa	An embodiment of the invention is the use of sbg36274SLITa, a member of human slit-like proteins, which may be necessary for CNS development, and therefore can be useful for diagnosis and treatment of nervous and muscular diseases. A close homolog of sbg36274SLITa is insulin-like growth factor. Insulin-like growth factorsmay be used to treat patients with growth hormone receptor deficiency (GHRD) (Fielder PJ, Gargosky SE, Vaccarello M, Wilson K, Cohen P, Diamond F, Guevara-Aguirre J, Rosenbloom AL, and Rosenfeld RG 1993. Acta Paediatr Suppl 388:40-3).	Cancer, infection, autoimmune disorder, hematopoietic disorder, wound healing disorder, inflammation, gastrointestinal ulceration, and diseases in spinal cord, thyroid gland, ovary, prostate, renal gland, small intestine, heart, trachea, thymus, lymph node, and muscular system

TABLE III Cont

Gene Name	Uses	Associated Diseases
sbg34575SLITa	An embodiment of the invention is the use of sbg34575SLITa, a member of human slit-like proteins, which may be necessary for CNS development, and therefore can be useful for diagnosis and treatment of nervous and muscular diseases. A close homolog of sbg34575SLITa is leucine-rich repeat proteins(BAA85972, mouse ISLR), which also demonstrates siginificant functions in neural development (Nagasawa, A., Kudoh, J., Noda, S., Mashima,Y., Wright, A., Oguchi,Y., and Shimizu, N. Genomics 61 (1), 37-43 ,1999). It has been shown that expression of slit genes is associated with neuronal migration in the developing forebrain (Hu H, Neuron 23:703-11,1999). It is thus possible that similar molecules play a crucial role in the morphogenesis of the mammalian nervous system (Taniguchi H, Tohyama M, Takagi T. Brain Res Mol Brain Res 1996 36(1):45-52).	Cancer, infection, autoimmune disorder, hematopoietic disorder, wound healing disorder, inflammation, gastrointestinal ulceration, and diseases in spinal cord, thyroid gland, ovary, prostate, small intestine, heart, trachea, thymus, lymph node, muscular system and colon
SBh71706.NIAP	An embodiment of the invention is the use of SBh71706.NIAP in the suppression of apoptosis. Related polypeptides have been used for treating regulation of cellular proliferation and differentiation and cell survival. The NIAP prevent motor neuron apoptosis induced by a variey of signals. These proteins do contain 3 BIR(Baculoviral Inhibitionof apoptosis protein repeats (LISTON,P.Nature 379 (6563), 349-353 (1996).	Autoimmune disorder, hematopoietic disorder, wound healing disorder, viral and bacterial infection, cancer, AIDS, amyotrophic lateral sclerosis, infertility, human spinal muscular atrophy and neurodegenerative disorder
SBh77492.Breast Specific BS200	An embodiment of the invention is the use of SBh77492.Breast Specific BS200 in regulating vascular smooth muscle cell proliferation.A close homolog of SBh77492.Breast Specific BS200 is EEGF protein. EEGF protein is useful for enhancing neurological functions or treating neoplasia and other disorders (LI HS and OLSEN H, New isolated extracellular/epidermal growth factor, Patent Accession Number W79739, HUMAN GENOME SCI INC).	Cancer, autoimmune disorders, wound healing disorders, infections, and hemotopoietic disorders
sbg115305LRRa	An embodiment of the invention is the use of sbg115305LRRa, a Leucine-rich repeat (LRR) protein, in neuronal development and the adult nervous systems as cell adhesion molecules. Close homologs of sbg115305LRRa are connectin, slit, chaoptin, and toll. These LRR proteins possibly have important roles in neuronal development and the adult nervous systems as cell adhesion molecules (Taguchi A, Wanaka A, Mori T, Matsumoto K, Imai Y, Tagaki T, Tohyama M, 1996, Brain Res Mol Brain Res 35:31-4). Leucine-rich repeat protein family has been implicated in protein-protein interactions, such as cell adhesion or receptor-ligand binding. At least one LRR was shown to be specifically expressed on B cells, suggesting its role in immunization (Miyake K, Yamashita Y, Ogata M, Sudo T, Kimoto M, 1995. J Immunol 154:3333-40). Some studies have shown that brain injury can cause over expression of neuronal LRR, suggesting that neuronal LRR may be an important component of the pathophysiological response to brain injury (Ishii N, Wanaka A, Tohyama M, Brain Res Mol Brain Res 1996 Aug;40(1):148-52).	Cancer, infection, autoimmune disorder, hematopoietic disorder, wound healing disorder, inflammation, gastrointestinal ulceration, diseases in spinal cord, thyroid gland, heart, trachea, thymus, lymph node, muscular system, and nervous system

Table IV. Quantitative, Tissue-specific mRNA expression detected using SybrMan

Quantitative, tissue-specific, mRNA expression patterns of the genes were measured using SYBR-Green Quantitative PCR (Applied Biosystems, Foster City, CA; see Schmittgen T.D. et al., Analytical Biochemistry 285:194-204, 2000) and human cDNAs prepared from various human tissues. Gene-specific PCR primers were designed using the first nucleic acid sequence listed in the Sequence List for each gene. Results are presented as the number of copies of each specific gene's mRNA detected in 1ng mRNA pool from each tissue. Two replicate mRNA measurements were made from each tissue RNA.

Gene Name	Tissue-Specific mRNA Expression (copies per ng mRNA; avg. ± range for 2 data points per tissue)									
	Brain	Heart	Lung	Liver	Kidney	Skeletal muscle	Intestine	Spleen/ lymph	Placenta	Testis
sbg10145 2SLITa	3389± 33	174± 11	187± 29	-6± 2	112± 4	64± 5	159± 7	147± 8	209± 37	563± 37
sbg29046 CYSa	338± 60	385± 69	735± 29	138± 41	592± 36	218± 25	186± 35	348± 52	839± 65	46124± 22605
sbg29046 CYSb	951± 69	1121± 74	358± 110	364± 44	871± 128	1133± 203	347± 101	612± 18	601± 12	591± 51
sbg37149 SLITb	4989± 18	51± 10	457± 41	148± 12	769± 90	17± 2	31± 11	37± 14	10± 6	346± 10
sbg36267 SLIta	2976± 186	258± 8	127± 30	2± 0	1374± 13	2188± 72	44± 1	81± 5	113± 4	242± 1
sbg35579 MELAa	4630± 1163	5518± 506	6114± 1422	1701± 140	5876± 1366	4017± 291	1918± 25	4310± 279	5247± 1	3589± 148
SBh69447 .Triglyceride Lipase	1± 0	5± 1	6± 6	-7± 6	3± 0	1± 0	-2± 3	4± 1	200± 8	18± 7
SBh86614 .Trypl	742± 82	392± 18	487± 24	642± 6	576± 12	369± 53	234± 15	547± 25	662± 2	550± 4
sbg106886 DELTAa	1308± 49	520± 19	340± 66	127± 11	418± 24	264± 39	130± 21	269± 21	538± 99	558± 116
sbg35779 THYa	2± 1	2± 1	21± 1	-4± 8	2± 1	-5± 8	26± 2	886± 38	7± 2	6± 5
sbg15130I NHa	4± 1	6± 2	209± 2	-4± 6	42± 1	-2± 8	9± 5	14± 0	12± 4	133± 9
SBh26548 .home-box	56± 3	85± 5	111± 18	273± 1	149± 12	80± 17	86± 12	88± 8	120± 49	81± 35
sbg26991 CERUa	1± 0	4± 2	2± 2	1± 3	4± 0	-1± 0	4± 0	2± 2	9± 0	26± 8
sbg35851 PEROa	83± 20	31± 1	37± 17	29± 5	53± 14	35± 8	17± 4	25± 13	36± 9	38± 3
sbg36274 SLITa	8770± 345	598± 8	591± 57	7± 5	518± 82	75± 9	253± 13	2847± 37	13± 1	278± 6
sbg34575 SLITa	2045± 346	2± 0	5± 0	-14± 2	-2± 4	-4± 3	0± 0	26± 7	10± 0	45± 6
SBh71706 .NIAP	251± 9	535± 25	1055± 55	122± 36	144± 7	322± 15	149± 5	1081± 67	740± 27	387± 17
SBh77492 .Breast Specific BS200	154± 4	134± 4	1954± 135	325± 57	981± 13	60± 6	700± 15	1246± 5	586± 30	2614± 69
sbg119652TYRa	43± 11	132± 21	25± 8	10± 7	122± 15	24± 10	22± 11	30± 8	15± 15	615± 4
sbg115305LRRa	7057± 326	289± 1	1122± 88	111± 4	547± 5	6178± 84	361± 12	896± 8	377± 18	9121± 120

Table V. Additional diseases based on mRNA expression in specific tissues

Tissue Expression	Additional Diseases
Brain	Neurological and psychiatric diseases, including Alzheimers, parasupranuclear palsey, Huntington's disease, myotonic dystrophy, anorexia, depression, schizophrenia, headache, amnesias, anxiety disorders, sleep disorders, multiple sclerosis
Heart	Cardiovascular diseases, including congestive heart failure, dilated cardiomyopathy, cardiac arrhythmias, Hodgson's Disease, myocardial infarction, cardiac arrhythmias
Lung	Respiratory diseases, including asthma, Chronic Obstructive Pulmonary Disease, cystic fibrosis, acute bronchitis, adult respiratory distress syndrome
Liver	Dyslipidemia, hypercholesterolemia, hypertriglyceridemia, cirrhosis, hepatic encephalopathy, fatty hepatocirrhosis, viral and nonviral hepatitis, Type II Diabetes Mellitis, impaired glucose tolerance
Kidney	Renal diseases, including acute and chronic renal failure, acute tubular necrosis, cystinuria, Fanconi's Syndrome, glomerulonephritis, renal cell carcinoma, renovascular hypertension
Skeletal muscle	Eulenburg's Disease, hypoglycemia, obesity, tendinitis, periodic paralyses, malignant hyperthermia, paramyotonia congenita, myotonia congenita
Intestine	Gastrointestinal diseases, including Myotonia congenita, Ileus, Intestinal Obstruction, Tropical Sprue, Pseudomembranous Enterocolitis
Spleen/lymph	Lymphangiectasia, hypersplenism, angiomas, ankylosing spondylitis, Hodgkin's Disease, macroglobulinemia, malignant lymphomas, rheumatoid arthritis
Placenta	Choriocarcinoma, hydatidiform mole, placenta previa
Testis	Testicular cancer, male reproductive diseases, including low testosterone and male infertility
Pancreas	Diabetic ketoacidosis, Type 1 & 2 diabetes, obesity, impaired glucose tolerance

What is claimed is:

1. An isolated polypeptide selected from the group consisting of:

(a) an isolated polypeptide encoded by a polynucleotide comprising a sequence set forth in Table I;

(b) an isolated polypeptide comprising a polypeptide sequence set forth in Table I; and

(c) a polypeptide sequence of a gene set forth in Table I.

2. An isolated polynucleotide selected from the group consisting of:

(a) an isolated polynucleotide comprising a polynucleotide sequence set forth in Table I;

(b) an isolated polynucleotide of a gene set forth in Table I;

(c) an isolated polynucleotide comprising a polynucleotide sequence encoding a polypeptide set forth in Table I;

(d) an isolated polynucleotide encoding a polypeptide set forth in Table I;

(e) a polynucleotide which is an RNA equivalent of the polynucleotide of (a) to (d);

or a polynucleotide sequence complementary to said isolated polynucleotide.

3. An expression vector comprising a polynucleotide capable of producing a polypeptide of claim 1 when said expression vector is present in a compatible host cell.

4. A process for producing a recombinant host cell which comprises the step of introducing an expression vector comprising a polynucleotide capable of producing a polypeptide of claim 1 into a cell such that the host cell, under appropriate culture conditions, produces said polypeptide.

5. A recombinant host cell produced by the process of claim 6.

6. A membrane of a recombinant host cell of claim 7 expressing said polypeptide.

7. A process for producing a polypeptide which comprises culturing a host cell of claim 7 under conditions sufficient for the production of said polypeptide and recovering said polypeptide from the culture.

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SMITHKLINE BEECHAM p.l.c.

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Leu Pro Ala Glu Arg Ser Gly Ala Arg His Lys Tyr Ser Leu Asn Gly
705 710 715 720
Glu Leu Lys Glu Tyr Tyr Cys Tyr Ile Asn Ser Pro Asn Thr Cys Gly
725 730 735
Leu Phe Pro Lys Arg Ser Met Ser Met Asn Val Met Phe Ile Gln Ser
740 745 750
Asp Cys Ser Asp Gly His Ser Gly Lys Ala Thr Leu Lys Phe
755 760 765

<210> 28
<211> 148
<212> PRT
<213> Homo sapiens

<400> 28
Ala Met Leu Gly Leu Pro Trp Lys Gly Gly Leu Ser Trp Ala Leu Leu
1 5 10 15
Leu Leu Leu Leu Gly Ser Gln Ile Leu Leu Ile Tyr Ala Trp His Phe
20 25 30
His Glu Gln Arg Asp Cys Asp Glu His Asn Val Met Ala Arg Tyr Leu
35 40 45
Pro Ala Thr Val Glu Phe Ala Val His Thr Phe Asn Gln Gln Ser Lys
50 55 60
Asp Tyr Tyr Ala Tyr Arg Leu Gly His Ile Leu Asn Ser Trp Lys Glu
65 70 75 80
Gln Val Glu Ser Lys Thr Val Phe Ser Met Glu Leu Leu Leu Gly Arg
85 90 95
Thr Arg Cys Gly Lys Phe Glu Asp Asp Ile Asp Asn Cys His Phe Gln
100 105 110
Glu Ser Thr Glu Leu Asn Asn Thr Phe Thr Cys Phe Phe Thr Ile Ser

115 120 125

Thr Arg Pro Trp Met Thr Gln Phe Ser Leu Leu Asn Lys Thr Cys Leu
130 135 140

Glu Gly Phe His
145

<210> 29
<211> 159
<212> PRT
<213> Homo sapiens

<400> 29

Asx Met Trp Ser Leu Pro Pro Ser Arg Ala Leu Ser Cys Ala Pro Leu
1 5 10 15

Leu Leu Leu Phe Ser Phe Gln Phe Leu Val Thr Tyr Ala Trp Arg Phe
20 25 30

Gln Glu Glu Glu Glu Trp Asn Asp Gln Lys Gln Ile Ala Val Tyr Leu
35 40 45

Pro Pro Thr Leu Glu Phe Ala Val Tyr Thr Phe Asn Lys Gln Ser Lys
50 55 60

Asp Trp Tyr Ala Tyr Lys Leu Val Pro Val Leu Ala Ser Trp Lys Glu
65 70 75 80

Gln Gly Tyr Asp Lys Met Thr Phe Ser Met Asn Leu Gln Leu Gly Arg
85 90 95

Thr Met Cys Gly Lys Phe Glu Asp Asp Ile Asp Asn Cys Pro Phe Gln
100 105 110

Glu Ser Pro Glu Leu Asn Asn Val Arg Gln Asp Thr Ser Phe Pro Pro
115 120 125

Gly Tyr Ser Cys Gly Cys Arg Met Gly Cys Gly Ala Asp Thr Asp Leu
130 135 140

His Leu Leu Leu His His Trp Asn Arg Ala Leu Glu Asp Thr Val
145 150 155

<210> 30
<211> 148
<212> PRT
<213> Homo sapiens

<400> 30

Asx Met Trp Ser Leu Pro Pro Ser Arg Ala Leu Ser Cys Ala Pro Leu
1 5 10 15

Leu Leu Leu Phe Ser Phe Gln Phe Leu Val Thr Tyr Ala Trp Arg Phe

```
                20                  25                  30
Gln Glu Glu Glu Glu Trp Asn Asp Gln Lys Gln Ile Ala Val Tyr Leu
        35                  40                  45
Pro Pro Thr Leu Glu Phe Ala Val Tyr Thr Phe Asn Lys Gln Ser Lys
    50                  55                  60
Asp Trp Tyr Ala Tyr Lys Leu Val Pro Val Leu Ala Ser Trp Lys Glu
65                  70                  75                  80
Gln Gly Tyr Asp Lys Met Thr Phe Ser Met Asn Leu Gln Leu Gly Arg
                85                  90                  95
Thr Met Cys Gly Lys Phe Glu Asp Asp Ile Asp Asn Cys Pro Phe Gln
            100                 105                 110
Glu Ser Pro Glu Leu Asn Asn Thr Cys Thr Cys Phe Phe Thr Ile Gly
        115                 120                 125
Ile Glu Pro Trp Arg Thr Arg Phe Asp Leu Trp Asn Lys Thr Cys Ser
    130                 135                 140
Gly Gly His Ser
145
```

<210> 31
<211> 820
<212> PRT
<213> Homo sapiens

<400> 31

```
Met Leu Arg Leu Gly Leu Cys Ala Ala Ala Leu Leu Cys Val Cys Arg
 1               5                  10                  15
Pro Gly Ala Val Arg Ala Asp Cys Trp Leu Ile Glu Gly Asp Lys Gly
            20                  25                  30
Tyr Val Trp Leu Ala Ile Cys Ser Gln Asn Gln Pro Pro Tyr Glu Thr
        35                  40                  45
Ile Pro Gln His Ile Asn Ser Thr Val His Asp Leu Arg Leu Asn Glu
    50                  55                  60
Asn Lys Leu Lys Ala Val Leu Tyr Ser Ser Leu Asn Arg Phe Gly Asn
65                  70                  75                  80
Leu Thr Asp Leu Asn Leu Thr Lys Asn Glu Ile Ser Tyr Ile Glu Asp
                85                  90                  95
Gly Ala Phe Leu Gly Gln Ser Ser Leu Gln Val Leu Gln Leu Gly Tyr
            100                 105                 110
Asn Lys Leu Ser Asn Leu Thr Glu Gly Met Leu Arg Gly Met Ser Arg
        115                 120                 125
Leu Gln Phe Leu Phe Val Gln His Asn Leu Ile Glu Val Val Thr Pro
    130                 135                 140
```

```
Thr Ala Phe Ser Glu Cys Pro Ser Leu Ile Ser Ile Asp Leu Ser Ser
145                 150                 155                 160
Asn Arg Leu Ser Arg Leu Asp Gly Ala Thr Phe Ala Ser Leu Ala Ser
                165                 170                 175
Leu Met Val Cys Glu Leu Ala Gly Asn Pro Phe Asn Cys Glu Cys Asp
            180                 185                 190
Leu Phe Gly Phe Leu Ala Trp Leu Val Val Phe Asn Asn Val Thr Lys
        195                 200                 205
Asn Tyr Asp Arg Leu Gln Cys Glu Ser Pro Arg Glu Phe Ala Gly Tyr
    210                 215                 220
Pro Leu Leu Val Pro Arg Pro Tyr His Ser Leu Asn Ala Ile Thr Val
225                 230                 235                 240
Leu Gln Ala Lys Cys Arg Asn Gly Ser Leu Pro Ala Arg Pro Val Ser
                245                 250                 255
His Pro Thr Pro Tyr Ser Thr Asp Ala Gln Arg Glu Pro Asp Glu Asn
            260                 265                 270
Ser Gly Phe Asn Pro Asp Glu Ile Leu Ser Val Glu Pro Pro Ala Ser
        275                 280                 285
Ser Thr Thr Asp Ala Ser Ala Gly Pro Ala Ile Lys Leu His His Val
    290                 295                 300
Thr Phe Thr Ser Ala Thr Leu Val Val Ile Ile Pro His Pro Tyr Ser
305                 310                 315                 320
Lys Met Tyr Ile Leu Val Gln Tyr Asn Asn Ser Tyr Phe Ser Asp Val
                325                 330                 335
Met Thr Leu Lys Asn Lys Lys Glu Ile Val Thr Leu Asp Lys Leu Arg
            340                 345                 350
Ala His Thr Glu Tyr Thr Phe Cys Val Thr Ser Leu Arg Asn Ser Arg
        355                 360                 365
Arg Phe Asn His Thr Cys Leu Thr Phe Thr Thr Arg Asp Pro Val Pro
    370                 375                 380
Gly Asp Leu Ala Pro Ser Thr Ser Thr Thr Thr His Tyr Ile Met Thr
385                 390                 395                 400
Ile Leu Gly Cys Leu Phe Gly Met Val Ile Val Leu Gly Ala Val Tyr
                405                 410                 415
Tyr Cys Leu Arg Lys Arg Arg Met Gln Glu Glu Lys Gln Lys Ser Val
            420                 425                 430
Asn Val Lys Lys Thr Ile Leu Glu Met Arg Tyr Gly Ala Asp Val Asp
        435                 440                 445
Ala Gly Ser Ile Val His Ala Ala Gln Lys Leu Gly Glu Pro Pro Val
    450                 455                 460
Leu Pro Val Ser Arg Met Ala Ser Ile Pro Ser Met Ile Gly Glu Lys
465                 470                 475                 480
```

Leu Pro Thr Ala Lys Gly Leu Glu Ala Gly Leu Asp Thr Pro Lys Val
485 490 495
Ala Thr Lys Gly Asn Tyr Ile Glu Val Arg Thr Gly Ala Gly Gly Asp
500 505 510
Gly Leu Ala Arg Pro Glu Asp Asp Leu Pro Asp Leu Glu Asn Gly Gln
515 520 525
Gly Ser Ala Ala Glu Ile Ser Thr Ile Ala Lys Glu Val Asp Lys Val
530 535 540
Asn Gln Ile Ile Asn Asn Cys Ile Asp Ala Leu Lys Leu Asp Ser Ala
545 550 555 560
Ser Phe Leu Gly Gly Gly Ser Ser Ser Gly Asp Pro Glu Leu Ala Phe
565 570 575
Glu Cys Gln Ser Leu Pro Ala Ala Ala Ala Ala Ser Ser Ala Thr Gly
580 585 590
Pro Gly Ala Leu Glu Arg Pro Ser Phe Leu Ser Pro Pro Tyr Lys Glu
595 600 605
Ser Ser His His Pro Leu Gln Arg Gln Leu Ser Ala Asp Ala Ala Val
610 615 620
Thr Arg Lys Thr Cys Ser Val Ser Ser Ser Gly Ser Ile Lys Ser Ala
625 630 635 640
Lys Val Phe Ser Leu Asp Val Pro Asp His Pro Ala Ala Thr Gly Leu
645 650 655
Ala Lys Gly Asp Ser Lys Tyr Ile Glu Lys Gly Ser Pro Leu Asn Ser
660 665 670
Pro Leu Asp Arg Leu Pro Leu Val Pro Ala Gly Ser Gly Gly Gly Ser
675 680 685
Gly Gly Gly Gly Gly Ile His His Leu Glu Val Lys Pro Ala Tyr His
690 695 700
Cys Ser Glu His Arg His Ser Phe Pro Ala Leu Tyr Tyr Glu Glu Gly
705 710 715 720
Ala Asp Ser Leu Ser Gln Arg Val Ser Phe Leu Lys Pro Leu Thr Arg
725 730 735
Ser Lys Arg Asp Ser Thr Tyr Ser Gln Leu Ser Pro Arg His Tyr Tyr
740 745 750
Ser Gly Tyr Ser Ser Ser Pro Glu Tyr Ser Ser Glu Ser Thr His Lys
755 760 765
Ile Trp Glu Arg Phe Arg Pro Tyr Lys Lys His His Arg Glu Glu Val
770 775 780
Tyr Met Ala Ala Gly His Ala Leu Arg Lys Lys Val Gln Phe Ala Lys
785 790 795 800
Asp Glu Asp Leu His Asp Ile Leu Asp Tyr Trp Lys Gly Val Ser Ala
805 810 815

Gln Gln Lys Leu
820

<210> 32
<211> 866
<212> PRT
<213> Homo sapiens

<400> 32

Met Thr Ile Glu Lys Met Phe Ser Phe Tyr Phe Leu Asp Tyr Phe Ser
1 5 10 15
Leu Phe Arg Ser Ile Gln Leu Phe Ala Asp Cys Lys Lys Met Phe Leu
20 25 30
Trp Leu Phe Leu Ile Leu Ser Ala Leu Ile Ser Ser Thr Asn Ala Asp
35 40 45
Ser Asp Ile Ser Val Glu Ile Cys Asn Val Cys Ser Cys Val Ser Val
50 55 60
Glu Asn Val Leu Tyr Val Asn Cys Glu Lys Val Ser Val Tyr Arg Pro
65 70 75 80
Asn Gln Leu Lys Pro Pro Trp Ser Asn Phe Tyr His Leu Asn Phe Gln
85 90 95
Asn Asn Phe Leu Asn Ile Leu Tyr Pro Asn Thr Phe Leu Asn Phe Ser
100 105 110
His Ala Val Ser Leu His Leu Gly Asn Asn Lys Leu Gln Asn Ile Glu
115 120 125
Gly Gly Ala Phe Leu Gly Leu Ser Ala Leu Lys Gln Leu His Leu Asn
130 135 140
Asn Asn Glu Leu Lys Ile Leu Arg Ala Asp Thr Phe Leu Gly Ile Glu
145 150 155 160
Asn Leu Glu Tyr Leu Gln Ala Asp Tyr Asn Leu Ile Lys Tyr Ile Glu
165 170 175
Arg Gly Ala Phe Asn Lys Leu His Lys Leu Lys Val Leu Ile Leu Asn
180 185 190
Asp Asn Leu Ile Ser Phe Leu Pro Asp Asn Ile Phe Arg Phe Ala Ser
195 200 205
Leu Thr His Leu Asp Ile Arg Gly Asn Arg Ile Gln Lys Leu Pro Tyr
210 215 220
Ile Gly Val Leu Glu His Ile Gly Arg Val Val Glu Leu Gln Leu Glu
225 230 235 240
Asp Asn Pro Trp Asn Cys Ser Cys Asp Leu Leu Pro Leu Lys Ala Trp
245 250 255
Leu Glu Asn Met Pro Tyr Asn Ile Tyr Ile Gly Glu Ala Ile Cys Glu

260 265 270

Thr Pro Ser Asp Leu Tyr Gly Arg Leu Leu Lys Glu Thr Asn Lys Gln

275 280 285

Glu Leu Cys Pro Met Gly Thr Gly Ser Asp Phe Asp Val Arg Ile Leu

290 295 300

Pro Pro Ser Gln Leu Glu Asn Gly Tyr Thr Thr Pro Asn Gly His Thr

305 310 315 320

Thr Gln Thr Ser Leu His Arg Leu Val Thr Lys Pro Pro Lys Thr Thr

325 330 335

Asn Pro Ser Lys Ile Ser Gly Ile Val Ala Gly Lys Ala Leu Ser Asn

340 345 350

Arg Asn Leu Ser Gln Ile Val Ser Tyr Gln Thr Arg Val Pro Pro Leu

355 360 365

Thr Pro Cys Pro Ala Pro Cys Phe Cys Lys Thr His Pro Ser Asp Leu

370 375 380

Gly Leu Ser Val Asn Cys Gln Glu Lys Asn Ile Gln Ser Met Ser Glu

385 390 395 400

Leu Ile Pro Lys Pro Leu Asn Ala Lys Lys Leu His Val Asn Gly Asn

405 410 415

Ser Ile Lys Asp Val Asp Val Ser Asp Phe Thr Asp Phe Glu Gly Leu

420 425 430

Asp Leu Leu His Leu Gly Ser Asn Gln Ile Thr Val Ile Lys Gly Asp

435 440 445

Val Phe His Asn Leu Thr Asn Leu Arg Arg Leu Tyr Leu Asn Gly Asn

450 455 460

Gln Ile Glu Arg Leu Tyr Pro Glu Ile Phe Ser Gly Leu His Asn Leu

465 470 475 480

Gln Tyr Leu Tyr Leu Glu Tyr Asn Leu Ile Lys Glu Ile Ser Ala Gly

485 490 495

Thr Phe Asp Ser Met Pro Asn Leu Gln Leu Leu Tyr Leu Asn Asn Asn

500 505 510

Leu Leu Lys Ser Leu Pro Val Tyr Ile Phe Ser Gly Ala Pro Leu Ala

515 520 525

Arg Leu Asn Leu Arg Asn Asn Lys Phe Met Tyr Leu Pro Val Ser Gly

530 535 540

Val Leu Asp Gln Leu Gln Ser Leu Thr Gln Ile Asp Leu Glu Gly Asn

545 550 555 560

Pro Trp Asp Cys Thr Cys Asp Leu Val Ala Leu Lys Leu Trp Val Glu

565 570 575

Lys Leu Ser Asp Gly Ile Val Val Lys Glu Leu Lys Cys Glu Thr Pro

580 585 590

Val Gln Phe Ala Asn Ile Glu Leu Lys Ser Leu Lys Asn Glu Ile Leu

595 600 605

Cys Pro Lys Leu Leu Asn Lys Pro Ser Ala Pro Phe Thr Ser Pro Ala
610 615 620

Pro Ala Ile Thr Phe Thr Thr Pro Leu Gly Pro Ile Arg Ser Pro Pro
625 630 635 640

Gly Gly Pro Val Pro Leu Ser Ile Leu Ile Leu Ser Ile Leu Val Val
645 650 655

Leu Ile Leu Thr Val Phe Val Ala Phe Cys Leu Leu Val Phe Val Leu
660 665 670

Arg Arg Asn Lys Lys Pro Thr Val Lys His Glu Gly Leu Gly Asn Pro
675 680 685

Asp Cys Gly Ser Met Gln Leu Gln Leu Arg Lys His Asp His Lys Thr
690 695 700

Asn Lys Lys Asp Gly Leu Ser Thr Glu Ala Phe Ile Pro Gln Thr Ile
705 710 715 720

Glu Gln Met Ser Lys Ser His Thr Cys Gly Leu Lys Glu Ser Glu Thr
725 730 735

Gly Phe Met Phe Ser Asp Pro Pro Gly Gln Lys Val Val Met Arg Asn
740 745 750

Val Ala Asp Lys Glu Lys Asp Leu Leu His Val Asp Thr Arg Lys Arg
755 760 765

Leu Ser Thr Ile Asp Glu Leu Asp Glu Leu Phe Pro Ser Arg Asp Ser
770 775 780

Asn Val Phe Ile Gln Asn Phe Leu Glu Ser Lys Lys Glu Tyr Asn Ser
785 790 795 800

Ile Gly Val Ser Gly Phe Glu Ile Arg Tyr Pro Glu Lys Gln Pro Asp
805 810 815

Lys Lys Ser Lys Lys Ser Leu Ile Gly Gly Asn His Ser Lys Ile Val
820 825 830

Val Glu Gln Arg Lys Ser Glu Tyr Phe Glu Leu Lys Ala Lys Leu Gln
835 840 845

Ser Ser Pro Asp Tyr Leu Gln Val Leu Glu Glu Gln Thr Ala Leu Asn
850 855 860

Lys Ile
865

<210> 33
<211> 533
<212> PRT
<213> Homo sapiens

<400> 33

```
Met Ala Pro Gly Pro Phe Ser Ser Ala Leu Leu Ser Pro Pro Pro Ala
 1               5                  10                  15
Ala Leu Pro Phe Leu Leu Leu Leu Trp Ala Gly Ala Ser Arg Gly Gln
            20                  25                  30
Pro Cys Pro Gly Arg Cys Ile Cys Gln Asn Val Ala Pro Thr Leu Thr
        35                  40                  45
Met Leu Cys Ala Lys Thr Gly Leu Leu Phe Val Pro Pro Ala Ile Asp
    50                  55                  60
Arg Arg Val Val Glu Leu Arg Leu Thr Asp Asn Phe Ile Ala Ala Val
65                  70                  75                  80
Arg Arg Arg Asp Phe Ala Asn Met Thr Ser Leu Val His Leu Thr Leu
                85                  90                  95
Ser Arg Asn Thr Ile Gly Gln Val Ala Ala Gly Ala Phe Ala Asp Leu
            100                 105                 110
Arg Ala Leu Arg Ala Leu His Leu Asp Ser Asn Arg Leu Ala Glu Val
        115                 120                 125
Arg Gly Asp Gln Leu Arg Gly Leu Gly Asn Leu Arg His Leu Ile Leu
    130                 135                 140
Gly Asn Asn Gln Ile Arg Arg Val Glu Ser Ala Ala Phe Asp Ala Phe
145                 150                 155                 160
Leu Ser Thr Val Glu Asp Leu Asp Leu Ser Tyr Asn Asn Leu Glu Ala
                165                 170                 175
Leu Pro Trp Glu Ala Val Gly Gln Met Val Asn Leu Asn Thr Leu Thr
            180                 185                 190
Leu Asp His Asn Leu Ile Asp His Ile Ala Glu Gly Thr Phe Val Gln
        195                 200                 205
Leu His Lys Leu Val Arg Leu Asp Met Thr Ser Asn Arg Leu His Lys
    210                 215                 220
Leu Pro Pro Asp Gly Leu Phe Leu Arg Ser Gln Gly Thr Gly Pro Lys
225                 230                 235                 240
Pro Pro Thr Pro Leu Thr Val Ser Phe Gly Gly Asn Pro Leu His Cys
                245                 250                 255
Asn Cys Glu Leu Leu Trp Leu Arg Arg Leu Thr Arg Glu Asp Asp Leu
            260                 265                 270
Glu Thr Cys Ala Thr Pro Glu His Leu Thr Asp Arg Tyr Phe Trp Ser
        275                 280                 285
Ile Pro Glu Glu Glu Phe Leu Cys Glu Pro Pro Leu Ile Thr Arg Gln
    290                 295                 300
Ala Gly Gly Arg Ala Leu Val Val Glu Gly Gln Ala Val Ser Leu Arg
305                 310                 315                 320
Cys Arg Ala Val Gly Asp Pro Glu Pro Val Val His Trp Val Ala Pro
                325                 330                 335
```

```
Asp Gly Arg Leu Leu Gly Asn Ser Ser Arg Thr Arg Val Arg Gly Asp
            340                 345                 350
Gly Thr Leu Asp Val Thr Ile Thr Thr Leu Arg Asp Ser Gly Thr Phe
        355                 360                 365
Thr Cys Ile Ala Ser Asn Ala Ala Gly Glu Ala Thr Ala Pro Val Glu
    370                 375                 380
Val Cys Val Val Pro Leu Pro Leu Met Ala Pro Pro Pro Ala Ala Pro
385                 390                 395                 400
Pro Pro Leu Thr Glu Pro Gly Ser Ser Asp Ile Ala Thr Pro Gly Arg
                405                 410                 415
Pro Gly Ala Asn Asp Ser Ala Ala Glu Arg Arg Leu Val Ala Ala Glu
            420                 425                 430
Leu Thr Ser Asn Ser Val Leu Ile Arg Trp Pro Ala Gln Arg Pro Val
        435                 440                 445
Pro Gly Ile Arg Met Tyr Gln Val Gln Tyr Asn Ser Ser Val Asp Asp
    450                 455                 460
Ser Leu Val Tyr Ser Ser Ala Ser Leu Met His Ile Val Glu His Gln
465                 470                 475                 480
Leu Asn Ala Ser Val Ile Cys Leu Ala Ser Pro Gly Asp Ala Ser Gly
                485                 490                 495
Ala Gly Ala Val Ser Leu Pro Val Glu Ser Leu Ser Ser Trp Leu Ser
            500                 505                 510
Asp Leu His Arg Glu Thr Cys Leu Leu Ala Ser Ile Ser Ala Phe Pro
        515                 520                 525
Val Phe Ser Trp Pro
    530
```

<210> 34
<211> 771
<212> PRT
<213> Homo sapiens

<400> 34

```
Met Ala Pro Gly Pro Phe Ser Ser Ala Leu Leu Ser Pro Pro Pro Ala
 1               5                  10                  15
Ala Leu Pro Phe Leu Leu Leu Leu Trp Ala Gly Ala Ser Arg Gly Gln
            20                  25                  30
Pro Cys Pro Gly Arg Cys Ile Cys Gln Asn Val Ala Pro Thr Leu Thr
        35                  40                  45
Met Leu Cys Ala Lys Thr Gly Leu Leu Phe Val Pro Pro Ala Ile Asp
    50                  55                  60
Arg Arg Val Val Glu Leu Arg Leu Thr Asp Asn Phe Ile Ala Ala Val
```

65 70 75 80
Arg Arg Arg Asp Phe Ala Asn Met Thr Ser Leu Val His Leu Thr Leu
85 90 95
Ser Arg Asn Thr Ile Gly Gln Val Ala Ala Gly Ala Phe Ala Asp Leu
100 105 110
Arg Ala Leu Arg Ala Leu His Leu Asp Ser Asn Arg Leu Ala Glu Val
115 120 125
Arg Gly Asp Gln Leu Arg Gly Leu Gly Asn Leu Arg His Leu Ile Leu
130 135 140
Gly Asn Asn Gln Ile Arg Arg Val Glu Ser Ala Ala Phe Asp Ala Phe
145 150 155 160
Leu Ser Thr Val Glu Asp Leu Asp Leu Ser Tyr Asn Asn Leu Glu Ala
165 170 175
Leu Pro Trp Glu Ala Val Gly Gln Met Val Asn Leu Asn Thr Leu Thr
180 185 190
Leu Asp His Asn Leu Ile Asp His Ile Ala Glu Gly Thr Phe Val Gln
195 200 205
Leu His Lys Leu Val Arg Leu Asp Met Thr Ser Asn Arg Leu His Lys
210 215 220
Leu Pro Pro Asp Gly Leu Phe Leu Arg Ser Gln Gly Thr Gly Pro Lys
225 230 235 240
Pro Pro Thr Pro Leu Thr Val Ser Phe Gly Gly Asn Pro Leu His Cys
245 250 255
Asn Cys Glu Leu Leu Trp Leu Arg Arg Leu Thr Arg Glu Asp Asp Leu
260 265 270
Glu Thr Cys Ala Thr Pro Glu His Leu Thr Asp Arg Tyr Phe Trp Ser
275 280 285
Ile Pro Glu Glu Glu Phe Leu Cys Glu Pro Pro Leu Ile Thr Arg Gln
290 295 300
Ala Gly Gly Arg Ala Leu Val Val Glu Gly Gln Ala Val Ser Leu Arg
305 310 315 320
Cys Arg Ala Val Gly Asp Pro Glu Pro Val Val His Trp Val Ala Pro
325 330 335
Asp Gly Arg Leu Leu Gly Asn Ser Ser Arg Thr Arg Val Arg Gly Asp
340 345 350
Gly Thr Leu Asp Val Thr Ile Thr Thr Leu Arg Asp Ser Gly Thr Phe
355 360 365
Thr Cys Ile Ala Ser Asn Ala Ala Gly Glu Ala Thr Ala Pro Val Glu
370 375 380
Val Cys Val Val Pro Leu Pro Leu Met Ala Pro Pro Pro Ala Ala Pro
385 390 395 400
Pro Pro Leu Thr Glu Pro Gly Ser Ser Asp Ile Ala Thr Pro Gly Arg

405 410 415
Pro Gly Ala Asn Asp Ser Ala Ala Glu Arg Arg Leu Val Ala Ala Glu
420 425 430
Leu Thr Ser Asn Ser Val Leu Ile Arg Trp Pro Ala Gln Arg Pro Val
435 440 445
Pro Gly Ile Arg Met Tyr Gln Val Gln Tyr Asn Ser Ser Val Asp Asp
450 455 460
Ser Leu Val Tyr Arg Met Ile Pro Ser Thr Ser Gln Thr Phe Leu Val
465 470 475 480
Asn Asp Leu Ala Ala Gly Arg Ala Tyr Asp Leu Cys Val Leu Ala Val
485 490 495
Tyr Asp Asp Gly Ala Thr Ala Leu Pro Ala Thr Arg Val Val Gly Cys
500 505 510
Val Gln Phe Thr Thr Ala Gly Asp Pro Ala Pro Cys Arg Pro Leu Arg
515 520 525
Ala His Phe Leu Gly Gly Thr Met Ile Ile Ala Ile Gly Gly Val Ile
530 535 540
Val Ala Ser Val Leu Val Phe Ile Val Leu Leu Met Ile Arg Tyr Lys
545 550 555 560
Val Tyr Gly Asp Gly Asp Ser Arg Arg Val Lys Gly Ser Arg Ser Leu
565 570 575
Pro Arg Val Ser His Val Cys Ser Gln Thr Asn Gly Ala Gly Thr Gly
580 585 590
Ala Ala Gln Ala Pro Ala Leu Pro Ala Gln Asp His Tyr Glu Ala Leu
595 600 605
Arg Glu Val Glu Ser Gln Ala Ala Pro Ala Val Ala Val Glu Ala Lys
610 615 620
Ala Met Glu Ala Glu Thr Ala Ser Ala Glu Pro Glu Val Val Leu Gly
625 630 635 640
Arg Ser Leu Gly Gly Ser Ala Thr Ser Leu Cys Leu Leu Pro Ser Glu
645 650 655
Glu Thr Ser Gly Glu Glu Ser Arg Ala Ala Val Gly Pro Arg Arg Ser
660 665 670
Arg Ser Gly Ala Leu Glu Pro Pro Thr Ser Ala Pro Pro Thr Leu Ala
675 680 685
Leu Val Pro Gly Gly Ala Ala Ala Arg Pro Arg Pro Gln Gln Arg Tyr
690 695 700
Ser Phe Asp Gly Asp Tyr Gly Ala Leu Phe Gln Ser His Ser Tyr Pro
705 710 715 720
Arg Arg Ala Arg Arg Thr Lys Arg His Arg Ser Thr Pro His Leu Asp
725 730 735
Gly Ala Gly Gly Gly Ala Ala Gly Glu Asp Gly Asp Leu Gly Leu Gly

740 745 750

Ser Ala Arg Ala Cys Leu Ala Phe Thr Ser Thr Glu Trp Met Leu Glu
755 760 765

Ser Thr Val
770

<210> 35
<211> 399
<212> PRT
<213> Homo sapiens

<400> 35

Met Trp Gln Leu Leu Ala Ala Ala Cys Trp Met Leu Leu Leu Gly Ser
1 5 10 15

Met Tyr Gly Tyr Asp Lys Lys Gly Asn Asn Ala Asn Pro Glu Ala Asn
20 25 30

Met Asn Ile Ser Gln Ile Ile Ser Tyr Trp Gly Tyr Pro Tyr Glu Glu
35 40 45

Tyr Asp Val Thr Thr Lys Asp Gly Tyr Ile Leu Gly Ile Tyr Arg Ile
50 55 60

Pro His Gly Arg Gly Cys Pro Gly Arg Thr Ala Pro Lys Pro Ala Val
65 70 75 80

Tyr Leu Gln His Gly Leu Ile Ala Ser Ala Ser Asn Trp Ile Cys Asn
85 90 95

Leu Pro Asn Asn Ser Leu Ala Phe Leu Leu Ala Asp Ser Gly Tyr Asp
100 105 110

Val Trp Leu Gly Asn Ser Arg Gly Asn Thr Trp Ser Arg Lys His Leu
115 120 125

Lys Leu Ser Pro Lys Ser Pro Glu Tyr Trp Ala Phe Ser Leu Asp Glu
130 135 140

Met Ala Lys Tyr Asp Leu Pro Ala Thr Ile Asn Phe Ile Ile Glu Lys
145 150 155 160

Thr Gly Gln Lys Arg Leu Tyr Tyr Val Gly His Ser Gln Gly Thr Thr
165 170 175

Ile Ala Phe Ile Ala Phe Ser Thr Asn Pro Glu Leu Ala Lys Lys Ile
180 185 190

Lys Ile Phe Phe Ala Leu Ala Pro Val Val Thr Val Lys Tyr Thr Gln
195 200 205

Ser Pro Met Lys Lys Leu Thr Thr Leu Ser Arg Arg Val Val Lys Val
210 215 220

Leu Phe Gly Asp Lys Met Phe His Pro His Thr Leu Phe Asp Gln Phe
225 230 235 240

Ile Ala Thr Lys Val Cys Asn Arg Lys Leu Phe Arg Arg Ile Cys Ser
245 250 255
Asn Phe Leu Phe Thr Leu Ser Gly Phe Asp Pro Gln Asn Leu Asn Met
260 265 270
Ser Arg Leu Asp Val Tyr Leu Ser His Asn Pro Ala Gly Thr Ser Val
275 280 285
Gln Asn Met Leu His Trp Ala Gln Ala Val Asn Ser Gly Gln Leu Gln
290 295 300
Ala Phe Asp Trp Gly Asn Ser Asp Gln Asn Met Met His Phe His Gln
305 310 315 320
Leu Thr Pro Pro Leu Tyr Asn Ile Thr Lys Ile Glu Val Pro Thr Ala
325 330 335
Ile Trp Asn Gly Gly Gln Asp Ile Val Ala Asp Pro Lys Asp Val Glu
340 345 350
Asn Leu Leu Pro Gln Ile Ala Asn Leu Ile Tyr Tyr Lys Leu Ile Pro
355 360 365
His Tyr Asn His Val Asp Phe Tyr Leu Gly Glu Asp Ala Pro Gln Glu
370 375 380
Ile Tyr Gln Asp Leu Ile Ile Leu Met Glu Glu Tyr Leu Gln Asn
385 390 395

<210> 36
<211> 255
<212> PRT
<213> Homo sapiens

<400> 36
Ile Val Gly Gly Ser Asn Ala Gln Pro Gly Thr Trp Pro Trp Gln Val
1 5 10 15
Ser Leu His His Gly Gly Gly His Ile Cys Gly Gly Ser Leu Ile Ala
20 25 30
Pro Ser Trp Val Leu Ser Ala Ala His Cys Phe Met Thr Gly Arg Gln
35 40 45
Tyr Arg Cys Pro Glu Thr Arg Arg Thr Arg Ser Ala Leu Pro Thr Arg
50 55 60
Lys Arg Arg Arg Ala Tyr Asn His Tyr Ser Gln Gly Ser Asp Leu Ala
65 70 75 80
Leu Leu Gln Leu Ala His Pro Thr Thr His Thr Pro Leu Cys Leu Pro
85 90 95
Gln Pro Ala His Arg Phe Pro Phe Gly Ala Ser Cys Trp Ala Thr Gly
100 105 110
Trp Asp Gln Asp Thr Ser Asp Ala Pro Ser Leu Ser Pro Ala Pro Gly

```
        115                 120                 125
Thr Leu Arg Asn Leu Arg Leu Arg Leu Ile Ser Arg Pro Thr Cys Asn
    130                 135                 140
Cys Ile Tyr Asn Gln Leu His Gln Arg His Leu Ser Asn Pro Ala Arg
145                 150                 155                 160
Pro Gly Met Leu Cys Gly Gly Pro Gln Pro Gly Val Gln Gly Pro Cys
                165                 170                 175
Gln Gly Leu Phe Gly Ala Pro Leu Val His Glu Val Arg Gly Thr Trp
            180                 185                 190
Phe Leu Ala Gly Leu His Ser Phe Gly Asp Ala Cys Gln Gly Pro Ala
        195                 200                 205
Arg Pro Ala Val Phe Thr Ala Leu Pro Ala Met Arg Thr Gly Ser Ala
    210                 215                 220
Val Trp Thr Arg Gln Val Tyr Phe Ala Glu Glu Pro Glu Pro Glu Ala
225                 230                 235                 240
Glu Pro Gly Ser Cys Leu Ala Asn Ile Arg Pro Phe Ser Leu Gln
                245                 250                 255
```

<210> 37
<211> 301
<212> PRT
<213> Homo sapiens

<400> 37

```
Met Glu Thr Ala Gly Ser Asp Trp Val Ala Gly Gly Pro Leu Thr Gln
 1               5                  10                  15
Ala Ser His Pro Ser Glu Cys Gly Lys Ala Pro Arg Pro Gly Ala Trp
            20                  25                  30
Pro Trp Glu Ala Gln Val Met Val Pro Gly Ser Arg Pro Cys His Gly
        35                  40                  45
Ala Leu Val Ser Glu Ser Trp Val Leu Ala Pro Ala Ser Cys Phe Leu
    50                  55                  60
Glu Gln Val Thr His Thr Leu Cys Cys Cys Arg Met Thr Arg Val Gly
65                  70                  75                  80
Ala Phe Cys Ala Arg Arg Arg Gly Pro Gly Phe Trp Leu Glu Ser Glu
                85                  90                  95
Thr Phe Pro Val Ala Val Tyr Leu Pro Arg Ala Tyr Asn His Tyr Ser
            100                 105                 110
Gln Gly Ser Asp Leu Ala Leu Leu Gln Leu Ala His Pro Thr Thr His
        115                 120                 125
Thr Pro Leu Cys Leu Pro Gln Pro Ala His Arg Phe Pro Phe Gly Ala
    130                 135                 140
```

Ser Cys Trp Ala Thr Gly Trp Asp Gln Asp Thr Ser Asp Ala Pro Gly
145 150 155 160
Thr Leu Arg Asn Leu Arg Leu Arg Leu Ile Ser Arg Pro Thr Cys Asn
165 170 175
Cys Ile Tyr Asn Gln Leu His Gln Arg His Leu Ser Asn Pro Ala Arg
180 185 190
Pro Gly Met Leu Cys Gly Gly Pro Gln Pro Gly Val Gln Gly Pro Cys
195 200 205
Gln Gly Leu Phe Gly Ala Pro Leu Val His Glu Val Arg Gly Thr Trp
210 215 220
Phe Leu Ala Gly Leu His Ser Phe Gly Asp Ala Cys Gln Gly Pro Ala
225 230 235 240
Arg Pro Ala Val Phe Thr Ala Leu Pro Ala Met Arg Thr Gly Ser Ala
245 250 255
Val Trp Thr Arg Gln Val Tyr Phe Ala Glu Glu Pro Glu Pro Glu Ala
260 265 270
Glu Pro Gly Ser Cys Leu Ala Asn Ile Ser Met Trp Pro Arg Gly Leu
275 280 285
Leu Pro Asn Pro Ala Ser Pro Gly Pro Phe Ser Leu Gln
290 295 300

<210> 38
<211> 383
<212> PRT
<213> Homo sapiens

<400> 38
Met Pro Ser Gly Cys Arg Cys Leu His Leu Val Cys Leu Leu Cys Ile
1 5 10 15
Leu Gly Ala Pro Gly Gln Pro Val Arg Ala Asp Asp Cys Ser Ser His
20 25 30
Cys Asp Leu Ala His Gly Cys Cys Ala Pro Asp Gly Ser Cys Arg Cys
35 40 45
Asp Pro Gly Trp Glu Gly Leu His Cys Glu Arg Cys Val Arg Met Pro
50 55 60
Gly Cys Gln His Gly Thr Cys His Gln Pro Trp Gln Cys Ile Cys His
65 70 75 80
Ser Gly Trp Ala Gly Lys Phe Cys Asp Lys Asp Glu His Ile Cys Thr
85 90 95
Thr Gln Ser Pro Cys Gln Asn Gly Gly Gln Cys Met Tyr Asp Gly Gly
100 105 110
Gly Glu Tyr His Cys Val Cys Leu Pro Gly Phe His Gly Arg Asp Cys

```
        115                 120                 125
Glu Arg Lys Ala Gly Pro Cys Glu Gln Ala Gly Ser Pro Cys Arg Asn
    130                 135                 140
Gly Gly Gln Cys Gln Asp Asp Gln Gly Phe Ala Leu Asn Phe Thr Cys
145                 150                 155                 160
Arg Cys Leu Val Gly Phe Val Gly Ala Arg Cys Glu Val Asn Val Asp
                165                 170                 175
Asp Cys Leu Met Arg Pro Cys Ala Asn Gly Ala Thr Cys Leu Asp Gly
            180                 185                 190
Ile Asn Arg Phe Ser Cys Leu Cys Pro Glu Gly Phe Ala Gly Arg Phe
        195                 200                 205
Cys Thr Ile Asn Leu Asp Asp Cys Ala Ser Arg Pro Cys Gln Arg Gly
    210                 215                 220
Ala Arg Cys Arg Asp Arg Val His Asp Phe Asp Cys Leu Cys Pro Ser
225                 230                 235                 240
Gly Tyr Gly Gly Lys Thr Cys Glu Leu Val Leu Pro Val Pro Asp Pro
                245                 250                 255
Pro Thr Thr Val Asp Thr Pro Leu Gly Pro Thr Ser Ala Val Val Val
            260                 265                 270
Pro Ala Thr Gly Pro Ala Pro His Ser Ala Gly Ala Gly Leu Leu Arg
        275                 280                 285
Ile Ser Val Lys Glu Val Val Arg Arg Gln Glu Ala Gly Leu Gly Glu
    290                 295                 300
Pro Ser Leu Val Ala Leu Val Val Phe Gly Ala Leu Thr Ala Ala Leu
305                 310                 315                 320
Val Leu Ala Thr Val Leu Leu Thr Leu Arg Ala Trp Arg Arg Gly Val
                325                 330                 335
Cys Pro Pro Gly Pro Cys Cys Tyr Pro Ala Pro His Tyr Ala Pro Ala
            340                 345                 350
Cys Gln Asp Gln Glu Cys Gln Val Ser Met Leu Pro Ala Gly Leu Pro
        355                 360                 365
Leu Pro Arg Asp Leu Pro Pro Glu Pro Gly Lys Thr Thr Ala Leu
    370                 375                 380
```

<210> 39
<211> 417
<212> PRT
<213> Homo sapiens

<400> 39

```
Met Ala Ser Tyr Leu Tyr Gly Val Leu Phe Ala Val Gly Leu Cys Ala
 1               5                  10                  15
```

Pro Ile Tyr Cys Val Ser Pro Ala Asn Ala Pro Ser Ala Tyr Pro Arg
20 25 30
Pro Ser Ser Thr Lys Ser Thr Pro Ala Ser Gln Val Tyr Ser Leu Asn
35 40 45
Thr Asp Phe Ala Phe Arg Leu Tyr Arg Arg Leu Val Leu Glu Thr Pro
50 55 60
Ser Gln Asn Ile Phe Phe Ser Pro Val Ser Val Ser Thr Ser Leu Ala
65 70 75 80
Met Leu Ser Leu Gly Ala His Ser Val Thr Lys Thr Gln Ile Leu Gln
85 90 95
Gly Leu Gly Phe Asn Leu Thr His Thr Pro Glu Ser Ala Ile His Gln
100 105 110
Gly Phe Gln His Leu Val His Ser Leu Thr Val Pro Ser Lys Asp Leu
115 120 125
Thr Leu Lys Met Gly Ser Ala Leu Phe Val Lys Lys Glu Leu Gln Leu
130 135 140
Gln Ala Asn Phe Leu Gly Asn Val Lys Arg Leu Tyr Glu Ala Glu Val
145 150 155 160
Phe Ser Thr Asp Phe Ser Asn Pro Ser Ile Ala Gln Ala Arg Ile Asn
165 170 175
Ser His Val Lys Lys Lys Thr Gln Gly Lys Val Val Asp Ile Ile Gln
180 185 190
Gly Leu Asp Leu Leu Thr Ala Met Val Leu Val Asn His Ile Phe Phe
195 200 205
Lys Ala Lys Trp Glu Lys Pro Phe His Pro Glu Tyr Thr Arg Lys Asn
210 215 220
Phe Pro Phe Leu Val Gly Glu Gln Val Thr Val His Val Pro Met Met
225 230 235 240
His Gln Lys Glu Gln Phe Ala Phe Gly Val Asp Thr Glu Leu Asn Cys
245 250 255
Phe Val Leu Gln Met Asp Tyr Lys Gly Asp Ala Val Ala Phe Phe Val
260 265 270
Leu Pro Ser Lys Gly Lys Met Arg Gln Leu Glu Gln Ala Leu Ser Ala
275 280 285
Arg Thr Leu Arg Lys Trp Ser His Ser Leu Gln Lys Arg Trp Ile Glu
290 295 300
Val Phe Ile Pro Arg Phe Ser Ile Ser Ala Ser Tyr Asn Leu Glu Thr
305 310 315 320
Ile Leu Pro Lys Met Gly Ile Gln Asn Val Phe Asp Lys Asn Ala Asp
325 330 335
Phe Ser Gly Ile Ala Lys Arg Asp Ser Leu Gln Val Ser Lys Ala Thr
340 345 350

```
His Lys Ala Val Leu Asp Val Ser Glu Glu Gly Thr Glu Ala Thr Ala
        355                 360                 365
Ala Thr Thr Thr Lys Phe Ile Val Arg Ser Lys Asp Gly Pro Ser Tyr
    370                 375                 380
Phe Thr Val Ser Phe Asn Arg Thr Phe Leu Met Met Ile Thr Asn Lys
385                 390                 395                 400
Ala Thr Asp Gly Ile Leu Phe Leu Gly Lys Val Glu Asn Pro Thr Lys
                405                 410                 415
Ser
```

<210> 40
<211> 243
<212> PRT
<213> Homo sapiens

<400> 40

```
Met Gly Ser Ser Ser Phe Leu Val Leu Met Val Ser Leu Val Leu Val
 1               5                  10                  15
Thr Leu Val Ala Val Glu Gly Val Lys Glu Gly Ile Glu Lys Ala Gly
            20                  25                  30
Val Cys Pro Ala Asp Asn Val Arg Cys Phe Lys Ser Asp Pro Pro Gln
        35                  40                  45
Cys His Thr Asp Gln Asp Cys Leu Gly Glu Arg Lys Cys Cys Tyr Leu
    50                  55                  60
His Cys Gly Phe Lys Cys Val Ile Pro Val Lys Glu Leu Glu Glu Gly
65                  70                  75                  80
Gln Arg Leu Leu His Asn Arg Glu Leu Pro Pro Ala Ala Ile Leu Gly
                85                  90                  95
Asp Ser Leu Thr Glu Lys Ser Gly Gly Cys Pro Pro Asp Asp Gly Pro
            100                 105                 110
Cys Leu Leu Ser Val Pro Asp Gln Cys Val Glu Asp Ser Gln Cys Pro
        115                 120                 125
Leu Thr Arg Lys Cys Cys Tyr Arg Ala Cys Phe Arg Gln Cys Val Pro
    130                 135                 140
Arg Val Ser Gly Lys Cys Leu Pro Ser Thr Leu Leu Thr Ile Gln Ala
145                 150                 155                 160
Pro Ser Phe Arg Ala Ser Gly Gln Gly Arg Ser Ser Pro Ser Ser Leu
                165                 170                 175
Cys Cys Ser Glu Ala Gly Gln Leu Pro Arg Gly Pro Thr Ala Leu Pro
            180                 185                 190
Gln Pro His Glu Pro Pro Val Ser Gln Gly Leu Arg Leu Leu Gly Gln
```

```
        195                 200                 205
Lys Ala Met Leu Pro Gln Arg Leu Arg Ala Gly Leu Pro Gly Ser Cys
    210                 215                 220
Gln Arg Tyr Gly Ser Trp Val Pro Arg Ala Gly Ala Ser Pro Leu Arg
225                 230                 235                 240
Ala Gln Leu
```

<210> 41
<211> 185
<212> PRT
<213> Homo sapiens

<400> 41

```
Met Gly Ser Ser Ser Phe Leu Val Leu Met Val Ser Leu Val Leu Val
 1               5                  10                  15
Thr Leu Val Ala Val Glu Gly Val Lys Glu Gly Ile Glu Lys Ala Gly
            20                  25                  30
Val Cys Pro Ala Asp Asn Val Arg Cys Phe Lys Ser Asp Pro Pro Gln
        35                  40                  45
Cys His Thr Asp Gln Asp Cys Leu Gly Glu Arg Lys Cys Cys Tyr Leu
    50                  55                  60
His Cys Gly Phe Lys Cys Val Ile Pro Val Lys Glu Leu Glu Glu Val
65                  70                  75                  80
Pro Cys Val Ala Val Lys Leu Gly Ser Cys Pro Glu Asp Gln Leu Arg
                85                  90                  95
Cys Leu Ser Pro Met Asn His Leu Cys His Lys Asp Ser Asp Cys Ser
            100                 105                 110
Gly Lys Lys Arg Cys Cys His Ser Ala Cys Gly Arg Asp Cys Arg Asp
        115                 120                 125
Pro Ala Arg Gly Thr Ala Pro Gly Cys Pro Gly Gln Val Pro Pro Leu
    130                 135                 140
Ser Glu Pro Ser Ser Asn Thr Phe Phe Ile Ala Thr Ser Leu Thr Gly
145                 150                 155                 160
Cys Leu Pro Arg Ser Gln Asp Leu Pro Trp Pro Gly Leu Gly Asn Trp
                165                 170                 175
Ile Gly Val Gly Gly Val Leu Leu Gly
            180                 185
```

<210> 42
<211> 198
<212> PRT

<213> Homo sapiens

<400> 42

Met Asn Ser Gly Arg Glu Pro Arg Thr Pro Arg Thr Leu Leu Ser Ile
1 5 10 15
Ala Asp Ile Leu Ala Pro Arg Met Val Pro Arg Ala Pro Ser Ala Pro
20 25 30
Gln Leu Pro Glu Ser Gly Pro Gly Pro Thr Ser Pro Leu Cys Ala Leu
35 40 45
Glu Glu Leu Thr Ser Lys Thr Phe Arg Gly Leu Asp Ala Arg Ala Leu
50 55 60
Gln Pro Ser Glu Gly Arg Ala Gly Pro Asp Ala Leu Gly Pro Gly Pro
65 70 75 80
Phe Gly Arg Lys Arg Arg Lys Ser Arg Thr Ala Phe Thr Ala Gln Gln
85 90 95
Val Leu Glu Leu Glu Arg Arg Phe Val Phe Gln Lys Tyr Leu Ala Pro
100 105 110
Ser Glu Arg Asp Gly Leu Ala Thr Arg Leu Gly Leu Ala Asn Ala Gln
115 120 125
Val Val Thr Trp Phe Gln Asn Arg Arg Ala Lys Leu Lys Arg Asp Val
130 135 140
Glu Glu Met Arg Ala Asp Val Ala Ser Leu Arg Ala Leu Ser Pro Glu
145 150 155 160
Val Leu Cys Ser Leu Ala Leu Pro Glu Gly Ala Pro Asp Pro Gly Leu
165 170 175
Cys Leu Gly Pro Ala Gly Pro Asp Ser Arg Pro His Leu Ser Asp Glu
180 185 190
Glu Ile Gln Val Asp Asp
195

<210> 43
<211> 330
<212> PRT
<213> Homo sapiens

<400> 43

Met Val Trp Lys Arg Glu Asn Phe Tyr Lys Glu Val Lys Arg Gly Arg
1 5 10 15
Ala Leu Phe Leu Lys Arg Leu Cys Ile Phe Asn Ile Asp Thr Asp Asn
20 25 30
Thr Phe Gln Arg Ile Ile Glu Lys Pro Ser Trp Leu Gly Phe Leu Gly
35 40 45

```
Pro Met Ile Lys Ala Glu Thr Gly Asp Phe Ile Tyr Val His Val Lys
    50                  55                  60
Asn Asn Ala Ser Arg Ala Tyr Ser Tyr His Pro His Gly Leu Thr Tyr
65                  70                  75                  80
Ser Lys Glu Asn Glu Gly Ala Ile Tyr Pro Asp Asn Thr Thr Gly Leu
                85                  90                  95
Gln Lys Glu Asp Glu Tyr Leu Glu Pro Gly Lys Gln Tyr Thr Tyr Lys
            100                 105                 110
Trp Tyr Val Glu Glu His Gln Gly Pro Gly Pro Asn Asp Ser Asn Cys
        115                 120                 125
Val Thr Arg Ile Tyr His Ser His Ile Asp Thr Ala Arg Asp Val Ala
    130                 135                 140
Ser Gly Leu Ile Gly Pro Ile Leu Thr Cys Lys Arg Ala Ile Asn Gly
145                 150                 155                 160
Tyr Ile Tyr Gly Asn Leu Pro Asn Leu Thr Met Cys Ala Glu Asp Arg
                165                 170                 175
Val Gln Trp Tyr Phe Val Gly Met Gly Gly Val Ala Asp Ile His Pro
            180                 185                 190
Val Tyr Leu Arg Gly Gln Thr Leu Ile Ser Arg Asn His Arg Lys Asp
        195                 200                 205
Thr Ile Met Leu Phe Pro Ser Ser Leu Glu Asp Ala Phe Met Val Ala
    210                 215                 220
Lys Ala Pro Gly Val Trp Met Leu Gly Cys Gln Ile His Gly Ser Asp
225                 230                 235                 240
Ile Leu Leu Leu Arg Asp Thr Lys Ser Glu Asn Phe Gln Gly Leu Ser
                245                 250                 255
Pro Phe His Met His Phe Leu Thr Asn Glu Glu Thr Tyr Ile Gln Glu
            260                 265                 270
Glu Ser Met Gln Ala Phe Phe Lys Val Ser Asn Cys Gln Lys Pro Ser
        275                 280                 285
Thr Glu Ala Phe Val Thr Gly Thr His Val Ile His Tyr Tyr Ile Ala
    290                 295                 300
Ala Lys Glu Ile Leu Trp Asn Tyr Ala Pro Ser Gly Ile Asp Phe Phe
305                 310                 315                 320
Thr Lys Lys Asn Leu Thr Ala Ala Gly Arg
                325                 330
```

<210> 44
<211> 479
<212> PRT
<213> Homo sapiens

<400> 44

Met Ala Ile Leu Pro Leu Leu Leu Cys Leu Leu Pro Leu Ala Pro Ala
1 5 10 15
Ser Ser Pro Pro Gln Ser Ala Thr Pro Ser Pro Cys Pro Arg Arg Cys
20 25 30
Arg Cys Gln Thr Gln Ser Leu Pro Leu Ser Val Leu Cys Pro Gly Ala
35 40 45
Gly Leu Leu Phe Val Pro Pro Ser Leu Asp Arg Arg Ala Ala Glu Leu
50 55 60
Arg Leu Ala Asp Asn Phe Ile Ala Ser Val Arg Arg Arg Asp Leu Ala
65 70 75 80
Asn Met Thr Gly Leu Leu His Leu Ser Leu Ser Arg Asn Thr Ile Arg
85 90 95
His Val Ala Ala Gly Ala Phe Ala Asp Leu Arg Ala Leu Arg Ala Leu
100 105 110
His Leu Asp Gly Asn Arg Leu Thr Ser Leu Gly Glu Gly Gln Leu Arg
115 120 125
Gly Leu Val Asn Leu Arg His Leu Ile Leu Ser Asn Asn Gln Leu Ala
130 135 140
Ala Leu Ala Ala Gly Ala Leu Asp Asp Cys Ala Glu Thr Leu Glu Asp
145 150 155 160
Leu Asp Leu Ser Tyr Asn Asn Leu Glu Gln Leu Pro Trp Glu Ala Leu
165 170 175
Gly Arg Leu Gly Asn Val Asn Thr Leu Gly Leu Asp His Asn Leu Leu
180 185 190
Ala Ser Val Pro Ala Gly Ala Phe Ser Arg Leu His Lys Leu Ala Arg
195 200 205
Leu Asp Met Thr Ser Asn Arg Leu Thr Thr Ile Pro Pro Asp Pro Leu
210 215 220
Phe Ser Arg Leu Pro Leu Leu Ala Arg Pro Arg Gly Ser Pro Ala Ser
225 230 235 240
Ala Leu Val Leu Ala Phe Gly Gly Asn Pro Leu His Cys Asn Cys Glu
245 250 255
Leu Val Trp Leu Arg Arg Leu Ala Arg Glu Asp Asp Leu Glu Ala Cys
260 265 270
Ala Ser Pro Pro Ala Leu Gly Gly Arg Tyr Phe Trp Ala Val Gly Glu
275 280 285
Glu Glu Phe Val Cys Glu Pro Pro Val Val Thr His Arg Ser Pro Pro
290 295 300
Leu Ala Val Pro Ala Gly Arg Pro Ala Ala Leu Arg Cys Arg Ala Val
305 310 315 320
Gly Asp Pro Glu Pro Arg Val Arg Trp Val Ser Pro Gln Gly Arg Leu

325 330 335
Leu Gly Asn Ser Ser Arg Ala Arg Ala Phe Pro Asn Gly Thr Leu Glu
340 345 350
Leu Leu Val Thr Glu Pro Gly Asp Gly Gly Ile Phe Thr Cys Ile Ala
355 360 365
Ala Asn Ala Ala Gly Glu Ala Thr Ala Ala Val Glu Leu Thr Val Gly
370 375 380
Pro Pro Pro Pro Pro Gln Leu Ala Asn Ser Thr Ser Cys Asp Pro Pro
385 390 395 400
Arg Asp Gly Asp Pro Asp Ala Leu Thr Pro Pro Ser Ala Ala Ser Ala
405 410 415
Ser Ala Lys Val Ala Asp Thr Gly Pro Pro Thr Asp Arg Gly Val Gln
420 425 430
Val Thr Glu His Gly Ala Thr Ala Ala Leu Val Gln Trp Pro Asp Gln
435 440 445
Arg Pro Ile Pro Gly Ile Arg Met Tyr Gln Ile Gln Tyr Asn Ser Ser
450 455 460
Ala Asp Asp Ile Leu Val Tyr Arg Cys Arg Val Gln Ala Leu Gly
465 470 475

<210> 45
<211> 628
<212> PRT
<213> Homo sapiens

<400> 45
Met Ala Ile Leu Pro Leu Leu Leu Cys Leu Leu Pro Leu Ala Pro Ala
1 5 10 15
Ser Ser Pro Pro Gln Ser Ala Thr Pro Ser Pro Cys Pro Arg Arg Cys
20 25 30
Arg Cys Gln Thr Gln Ser Leu Pro Leu Ser Val Leu Cys Pro Gly Ala
35 40 45
Gly Leu Leu Phe Val Pro Pro Ser Leu Asp Arg Arg Ala Ala Glu Leu
50 55 60
Arg Leu Ala Asp Asn Phe Ile Ala Ser Val Arg Arg Arg Asp Leu Ala
65 70 75 80
Asn Met Thr Gly Leu Leu His Leu Ser Leu Ser Arg Asn Thr Ile Arg
85 90 95
His Val Ala Ala Gly Ala Phe Ala Asp Leu Arg Ala Leu Arg Ala Leu
100 105 110
His Leu Asp Gly Asn Arg Leu Thr Ser Leu Gly Glu Gly Gln Leu Arg
115 120 125

```
Gly Leu Val Asn Leu Arg His Leu Ile Leu Ser Asn Asn Gln Leu Ala
    130                 135                 140
Ala Leu Ala Ala Gly Ala Leu Asp Asp Cys Ala Glu Thr Leu Glu Asp
145                 150                 155                 160
Leu Asp Leu Ser Tyr Asn Asn Leu Glu Gln Leu Pro Trp Glu Ala Leu
                165                 170                 175
Gly Arg Leu Gly Asn Val Asn Thr Leu Gly Leu Asp His Asn Leu Leu
            180                 185                 190
Ala Ser Val Pro Ala Gly Ala Phe Ser Arg Leu His Lys Leu Ala Arg
        195                 200                 205
Leu Asp Met Thr Ser Asn Arg Leu Thr Thr Ile Pro Pro Asp Pro Leu
    210                 215                 220
Phe Ser Arg Leu Pro Leu Leu Ala Arg Pro Arg Gly Ser Pro Ala Ser
225                 230                 235                 240
Ala Leu Val Leu Ala Phe Gly Gly Asn Pro Leu His Cys Asn Cys Glu
                245                 250                 255
Leu Val Trp Leu Arg Arg Leu Ala Arg Glu Asp Asp Leu Glu Ala Cys
            260                 265                 270
Ala Ser Pro Pro Ala Leu Gly Gly Arg Tyr Phe Trp Ala Val Gly Glu
        275                 280                 285
Glu Glu Phe Val Cys Glu Pro Pro Val Val Thr His Arg Ser Pro Pro
    290                 295                 300
Leu Ala Val Pro Ala Gly Arg Pro Ala Ala Leu Arg Cys Arg Ala Val
305                 310                 315                 320
Gly Asp Pro Glu Pro Arg Val Arg Trp Val Ser Pro Gln Gly Arg Leu
                325                 330                 335
Leu Gly Asn Ser Ser Arg Ala Arg Ala Phe Pro Asn Gly Thr Leu Glu
            340                 345                 350
Leu Leu Val Thr Glu Pro Gly Asp Gly Gly Ile Phe Thr Cys Ile Ala
        355                 360                 365
Ala Asn Ala Ala Gly Glu Ala Thr Ala Ala Val Glu Leu Thr Val Gly
    370                 375                 380
Pro Pro Pro Pro Pro Gln Leu Ala Asn Ser Thr Ser Cys Asp Pro Pro
385                 390                 395                 400
Arg Asp Gly Asp Pro Asp Ala Leu Thr Pro Pro Ser Ala Ala Ser Ala
                405                 410                 415
Ser Ala Lys Val Ala Asp Thr Gly Pro Pro Thr Asp Arg Gly Val Gln
            420                 425                 430
Val Thr Glu His Gly Ala Thr Ala Ala Leu Val Gln Trp Pro Asp Gln
        435                 440                 445
Arg Pro Ile Pro Gly Ile Arg Met Tyr Gln Ile Gln Tyr Asn Ser Ser
    450                 455                 460
```

Ala Asp Asp Ile Leu Val Tyr Arg Met Ile Pro Ala Glu Ser Arg Ser
465 470 475 480
Phe Leu Leu Thr Asp Leu Ala Ser Gly Arg Thr Tyr Asp Leu Cys Val
485 490 495
Leu Ala Val Tyr Glu Asp Ser Ala Thr Gly Leu Thr Ala Thr Arg Pro
500 505 510
Val Gly Cys Ala Arg Phe Ser Thr Glu Pro Ala Leu Arg Pro Cys Gly
515 520 525
Ala Pro His Ala Pro Phe Leu Gly Gly Thr Met Ile Ile Ala Leu Gly
530 535 540
Gly Val Ile Val Ala Ser Val Leu Val Phe Ile Phe Val Leu Leu Met
545 550 555 560
Arg Tyr Lys Val His Gly Gly Gln Pro Pro Gly Lys Ala Lys Ile Pro
565 570 575
Ala Pro Val Ser Ser Val Cys Ser Gln Thr Asn Gly Ala Leu Gly Pro
580 585 590
Thr Pro Thr Pro Ala Pro Pro Ala Pro Glu Pro Ala Ala Leu Arg Ala
595 600 605
His Thr Val Val Gln Leu Asp Cys Glu Pro Trp Gly Pro Gly His Glu
610 615 620
Pro Val Gly Pro
625

<210> 46
<211> 845
<212> PRT
<213> Homo sapiens

<400> 46
Met Leu Ser Gly Val Trp Phe Leu Ser Val Leu Thr Val Ala Gly Ile
1 5 10 15
Leu Gln Thr Glu Ser Arg Lys Thr Ala Lys Asp Ile Cys Lys Ile Arg
20 25 30
Cys Leu Cys Glu Glu Lys Glu Asn Val Leu Asn Ile Asn Cys Glu Asn
35 40 45
Lys Gly Phe Thr Thr Val Ser Leu Leu Gln Pro Pro Gln Tyr Arg Ile
50 55 60
Tyr Gln Leu Phe Leu Asn Gly Asn Leu Leu Thr Arg Leu Tyr Pro Asn
65 70 75 80
Glu Phe Val Asn Tyr Ser Asn Ala Val Thr Leu His Leu Gly Asn Asn
85 90 95
Gly Leu Gln Glu Ile Arg Thr Gly Ala Phe Ser Gly Leu Lys Thr Leu

100 105 110
Lys Arg Leu His Leu Asn Asn Asn Lys Leu Glu Ile Leu Arg Glu Asp
115 120 125
Thr Phe Leu Gly Leu Glu Ser Leu Glu Tyr Leu Gln Ala Asp Tyr Asn
130 135 140
Tyr Ile Ser Ala Ile Glu Ala Gly Ala Phe Ser Lys Leu Asn Lys Leu
145 150 155 160
Lys Val Leu Ile Leu Asn Asp Asn Leu Leu Leu Ser Leu Pro Ser Asn
165 170 175
Val Phe Arg Phe Val Leu Leu Thr His Leu Asp Leu Arg Gly Asn Arg
180 185 190
Leu Lys Val Met Pro Phe Ala Gly Val Leu Glu His Ile Gly Gly Ile
195 200 205
Met Glu Ile Gln Leu Glu Glu Asn Pro Trp Asn Cys Thr Cys Asp Leu
210 215 220
Leu Pro Leu Lys Ala Trp Leu Asp Thr Ile Thr Val Phe Val Gly Glu
225 230 235 240
Ile Val Cys Glu Thr Pro Phe Arg Leu His Gly Lys Asp Val Thr Gln
245 250 255
Leu Thr Arg Gln Asp Leu Cys Pro Arg Lys Ser Ala Ser Asp Ser Ser
260 265 270
Gln Arg Gly Ser His Ala Asp Thr His Val Gln Arg Leu Ser Pro Thr
275 280 285
Met Asn Pro Ala Leu Asn Pro Thr Arg Ala Pro Lys Ala Ser Arg Pro
290 295 300
Pro Lys Met Arg Asn Arg Pro Thr Pro Arg Val Thr Val Ser Lys Asp
305 310 315 320
Arg Gln Ser Phe Gly Pro Ile Met Val Tyr Gln Thr Lys Ser Pro Val
325 330 335
Pro Leu Thr Cys Pro Ser Ser Cys Val Cys Thr Ser Gln Ser Ser Asp
340 345 350
Asn Gly Leu Asn Val Asn Cys Gln Glu Arg Lys Phe Thr Asn Ile Ser
355 360 365
Asp Leu Gln Pro Lys Pro Thr Ser Pro Lys Lys Leu Tyr Leu Thr Gly
370 375 380
Asn Tyr Leu Gln Thr Val Tyr Lys Asn Asp Leu Leu Glu Tyr Ser Ser
385 390 395 400
Leu Asp Leu Leu His Leu Gly Asn Asn Arg Ile Ala Val Ile Gln Glu
405 410 415
Gly Ala Phe Thr Asn Leu Thr Ser Leu Arg Arg Leu Tyr Leu Asn Gly
420 425 430
Asn Tyr Leu Glu Val Leu Tyr Pro Ser Met Phe Asp Gly Leu Gln Ser

435 440 445

Leu Gln Tyr Leu Tyr Leu Glu Tyr Asn Val Ile Lys Glu Ile Lys Pro
450 455 460

Leu Thr Phe Asp Ala Leu Ile Asn Leu Gln Leu Leu Phe Leu Asn Asn
465 470 475 480

Asn Leu Leu Arg Ser Leu Pro Asp Asn Ile Phe Gly Gly Thr Ala Leu
485 490 495

Thr Arg Leu Asn Leu Arg Asn Asn His Phe Ser His Leu Pro Val Lys
500 505 510

Gly Val Leu Asp Gln Leu Pro Ala Phe Ile Gln Ile Asp Leu Gln Glu
515 520 525

Asn Pro Trp Asp Cys Thr Cys Asp Ile Met Gly Leu Lys Asp Trp Thr
530 535 540

Glu His Ala Asn Ser Pro Val Ile Ile Asn Glu Val Thr Cys Glu Ser
545 550 555 560

Pro Ala Lys His Ala Gly Glu Ile Leu Lys Phe Leu Gly Arg Glu Ala
565 570 575

Ile Cys Pro Asp Ser Pro Asn Leu Ser Asp Gly Thr Val Leu Ser Met
580 585 590

Asn His Asn Thr Asp Thr Pro Arg Ser Leu Ser Val Ser Pro Ser Ser
595 600 605

Tyr Pro Glu Leu His Thr Glu Val Pro Leu Ser Val Leu Ile Leu Gly
610 615 620

Leu Leu Val Val Phe Ile Leu Ser Val Cys Phe Gly Ala Gly Leu Phe
625 630 635 640

Val Phe Val Leu Lys Arg Arg Lys Gly Val Pro Ser Val Pro Arg Asn
645 650 655

Thr Asn Asn Leu Asp Val Ser Ser Phe Gln Leu Gln Tyr Gly Ser Tyr
660 665 670

Asn Thr Glu Thr His Asp Lys Thr Asp Gly His Val Tyr Asn Tyr Ile
675 680 685

Pro Pro Pro Val Gly Gln Met Cys Gln Asn Pro Ile Tyr Met Gln Lys
690 695 700

Glu Gly Asp Pro Val Ala Tyr Tyr Arg Asn Leu Gln Glu Phe Ser Tyr
705 710 715 720

Ser Asn Leu Glu Glu Lys Lys Glu Glu Pro Ala Thr Pro Ala Tyr Thr
725 730 735

Ile Ser Ala Thr Glu Leu Leu Glu Lys Gln Ala Thr Pro Arg Glu Pro
740 745 750

Glu Leu Leu Tyr Gln Asn Ile Ala Glu Arg Val Lys Glu Leu Pro Ser
755 760 765

Ala Gly Leu Val His Tyr Asn Phe Cys Thr Leu Pro Lys Arg Gln Phe

770 775 780

Ala Pro Ser Tyr Glu Ser Arg Arg Gln Asn Gln Asp Arg Ile Asn Lys
785 790 795 800
Thr Val Leu Tyr Gly Thr Pro Arg Lys Cys Phe Val Gly Gln Ser Lys
805 810 815
Pro Asn His Pro Leu Leu Gln Ala Lys Pro Gln Ser Glu Pro Asp Tyr
820 825 830
Leu Glu Val Leu Glu Lys Gln Thr Ala Ile Ser Gln Leu
835 840 845

<210> 47
<211> 349
<212> PRT
<213> Homo sapiens

<400> 47
Met Gly Ile Thr Cys Trp Ile Ala Leu Tyr Ala Val Glu Ala Leu Pro
1 5 10 15
Thr Cys Pro Phe Ser Cys Lys Cys Asp Ser Arg Ser Leu Glu Val Asp
20 25 30
Cys Ser Gly Leu Gly Leu Thr Thr Val Pro Pro Asp Val Pro Ala Ala
35 40 45
Thr Arg Thr Leu Leu Leu Leu Asn Asn Lys Leu Ser Ala Leu Pro Ser
50 55 60
Trp Ala Phe Ala Asn Leu Ser Ser Leu Gln Arg Leu Asp Leu Ser Asn
65 70 75 80
Asn Phe Leu Asp Arg Leu Pro Arg Ser Ile Phe Gly Asp Leu Thr Asn
85 90 95
Leu Thr Glu Leu Gln Leu Arg Asn Asn Ser Ile Arg Thr Leu Asp Arg
100 105 110
Asp Leu Leu Arg His Ser Pro Leu Leu Arg His Leu Asp Leu Ser Ile
115 120 125
Asn Gly Leu Ala Gln Leu Pro Pro Gly Leu Phe Asp Gly Leu Leu Ala
130 135 140
Leu Arg Ser Leu Ser Leu Arg Ser Asn Arg Leu Gln Asn Leu Asp Arg
145 150 155 160
Leu Thr Phe Glu Pro Leu Ala Asn Leu Gln Leu Leu Gln Val Gly Asp
165 170 175
Asn Pro Trp Glu Cys Asp Cys Asn Leu Arg Glu Phe Lys His Trp Met
180 185 190
Glu Trp Phe Ser Tyr Arg Gly Gly Arg Leu Asp Gln Leu Ala Cys Thr
195 200 205

```
Leu Pro Lys Glu Leu Arg Gly Lys Asp Met Arg Met Val Pro Met Glu
    210                 215                 220
Met Phe Asn Tyr Cys Ser Gln Leu Glu Asp Glu Asn Ser Ser Ala Gly
225                 230                 235                 240
Leu Asp Ile Pro Gly Pro Pro Cys Thr Lys Ala Ser Pro Glu Pro Ala
                245                 250                 255
Lys Pro Lys Pro Gly Ala Glu Pro Glu Pro Glu Pro Ser Thr Ala Cys
            260                 265                 270
Pro Gln Lys Gln Arg His Arg Pro Ala Ser Val Arg Arg Ala Met Gly
        275                 280                 285
Thr Val Ile Ile Ala Gly Val Val Cys Gly Val Val Cys Ile Met Met
    290                 295                 300
Val Val Ala Ala Ala Tyr Gly Cys Ile Tyr Ala Ser Leu Met Ala Lys
305                 310                 315                 320
Tyr His Arg Glu Leu Lys Lys Arg Gln Pro Leu Met Gly Asp Pro Glu
                325                 330                 335
Gly Glu His Glu Asp Gln Lys Gln Ile Ser Ser Val Ala
            340                 345
```

<210> 48
<211> 738
<212> PRT
<213> Homo sapiens

<400> 48

```
Met Gly Met Thr Val Ile Lys Gln Ile Thr Asp Asp Leu Phe Val Trp
 1               5                  10                  15
Asn Val Leu Asn Arg Glu Glu Val Asn Ile Ile Cys Cys Glu Lys Val
            20                  25                  30
Glu Gln Asp Ala Ala Arg Gly Ile Ile His Met Ile Leu Lys Lys Gly
        35                  40                  45
Ser Glu Ser Cys Asn Leu Phe Leu Lys Ser Leu Lys Glu Trp Asn Tyr
    50                  55                  60
Pro Leu Phe Gln Asp Leu Asn Gly Gln Ser Leu Phe His Gln Thr Ser
65                  70                  75                  80
Glu Gly Asp Leu Asp Asp Leu Ala Gln Asp Leu Lys Asp Leu Tyr His
                85                  90                  95
Thr Pro Ser Phe Leu Asn Phe Tyr Pro Leu Gly Glu Asp Ile Asp Ile
            100                 105                 110
Ile Phe Asn Leu Lys Ser Thr Phe Thr Glu Pro Val Leu Trp Arg Lys
        115                 120                 125
Asp Gln His His His Arg Val Glu Gln Leu Thr Leu Asn Gly Leu Leu
```

130 135 140

Gln Ala Leu Gln Ser Pro Cys Ile Ile Glu Gly Glu Ser Gly Lys Gly
145 150 155 160
Lys Ser Thr Leu Leu Gln Arg Ile Ala Met Leu Trp Gly Ser Gly Lys
165 170 175
Cys Lys Ala Leu Thr Lys Phe Lys Phe Val Phe Phe Leu Arg Leu Ser
180 185 190
Arg Ala Gln Gly Gly Leu Phe Glu Thr Leu Cys Asp Gln Leu Leu Asp
195 200 205
Ile Pro Gly Thr Ile Arg Lys Gln Thr Phe Met Ala Met Leu Leu Lys
210 215 220
Leu Arg Gln Arg Val Leu Phe Leu Leu Asp Gly Tyr Asn Glu Phe Lys
225 230 235 240
Pro Gln Asn Cys Pro Glu Ile Glu Ala Leu Ile Lys Glu Asn His Arg
245 250 255
Phe Lys Asn Met Val Ile Val Thr Thr Thr Thr Glu Cys Leu Arg His
260 265 270
Ile Arg Gln Phe Gly Ala Leu Thr Ala Glu Val Gly Asp Met Thr Glu
275 280 285
Asp Ser Ala Gln Ala Leu Ile Arg Glu Val Leu Ile Lys Glu Leu Ala
290 295 300
Glu Gly Leu Leu Leu Gln Ile Gln Lys Ser Arg Cys Leu Arg Asn Leu
305 310 315 320
Met Lys Thr Pro Leu Phe Val Val Ile Thr Cys Ala Ile Gln Met Gly
325 330 335
Glu Ser Glu Phe His Ser His Thr Gln Thr Thr Leu Phe His Thr Phe
340 345 350
Tyr Asp Leu Leu Ile Gln Lys Asn Lys His Lys His Lys Gly Val Ala
355 360 365
Ala Ser Asp Phe Ile Arg Ser Leu Asp His Cys Gly Asp Leu Ala Leu
370 375 380
Glu Gly Val Phe Ser His Lys Phe Asp Phe Glu Leu Gln Asp Val Ser
385 390 395 400
Ser Val Asn Glu Asp Val Leu Leu Thr Thr Gly Leu Leu Cys Lys Tyr
405 410 415
Thr Ala Gln Arg Phe Lys Pro Lys Tyr Lys Phe Phe His Lys Ser Phe
420 425 430
Gln Glu Tyr Thr Ala Gly Arg Arg Leu Ser Ser Leu Leu Thr Ser His
435 440 445
Glu Pro Glu Glu Val Thr Lys Gly Asn Gly Tyr Leu Gln Lys Met Val
450 455 460
Ser Ile Ser Asp Ile Thr Ser Thr Tyr Ser Ser Leu Leu Arg Tyr Thr

```
465                 470                 475                 480
Cys Gly Ser Ser Val Glu Ala Thr Arg Ala Val Met Lys His Leu Ala
                485                 490                 495
Ala Val Tyr Gln His Gly Cys Leu Leu Gly Leu Ser Ile Ala Lys Arg
            500                 505                 510
Pro Leu Trp Arg Gln Glu Ser Leu Gln Ser Val Lys Asn Thr Thr Glu
        515                 520                 525
Gln Glu Ile Leu Lys Ala Ile Asn Ile Asn Ser Phe Val Glu Cys Gly
    530                 535                 540
Ile His Leu Tyr Gln Glu Ser Thr Ser Lys Ser Ala Leu Ser Gln Glu
545                 550                 555                 560
Phe Glu Ala Phe Phe Gln Gly Lys Ser Leu Tyr Ile Asn Ser Gly Asn
                565                 570                 575
Ile Pro Asp Tyr Leu Phe Asp Phe Phe Glu His Leu Pro Asn Cys Ala
            580                 585                 590
Ser Ala Leu Asp Phe Ile Lys Leu Asp Phe Tyr Gly Gly Ala Met Ala
        595                 600                 605
Ser Trp Glu Lys Ala Ala Glu Asp Thr Gly Gly Ile His Met Glu Glu
    610                 615                 620
Ala Pro Glu Thr Tyr Ile Pro Ser Arg Ala Val Ser Leu Phe Phe Asn
625                 630                 635                 640
Trp Lys Gln Glu Phe Arg Thr Leu Glu Val Thr Leu Arg Asp Phe Ser
                645                 650                 655
Lys Leu Asn Lys Gln Asp Ile Arg Tyr Leu Gly Lys Ile Phe Ser Ser
            660                 665                 670
Ala Thr Ser Leu Arg Leu Gln Ile Lys Arg Cys Ala Gly Val Ala Gly
        675                 680                 685
Ser Leu Ser Leu Val Leu Ser Thr Cys Lys Asn Ile Tyr Ser Leu Met
    690                 695                 700
Val Glu Ala Ser Pro Leu Thr Ile Glu Asp Glu Arg His Ile Thr Ser
705                 710                 715                 720
Val Thr Asn Leu Lys Thr Leu Ser Ile His Asp Leu Gln Asn Gln Arg
                725                 730                 735
Leu Pro
```

<210> 49
<211> 1070
<212> PRT
<213> Homo sapiens

<400> 49

```
Met Tyr Lys Ser Leu Asn Ile Asp Glu Cys Asp Leu His Ala Trp Leu
 1               5                  10                  15
Asp Leu Pro Ala Glu Lys Pro Leu Gly Val Val Asn Arg Val Cys Trp
            20                  25                  30
Gly Phe Ile Arg Phe Lys Gly Tyr Met Tyr Pro Leu Asp Tyr Leu Asn
        35                  40                  45
Phe Ile Lys Asp Asn Ser Arg Ala Leu Ile Gln Arg Met Gly Met Thr
    50                  55                  60
Val Ile Lys Gln Ile Thr Asp Asp Leu Phe Val Trp Asn Val Leu Asn
65                  70                  75                  80
Arg Glu Glu Val Asn Ile Ile Cys Cys Glu Lys Val Glu Gln Asp Ala
                85                  90                  95
Ala Arg Gly Ile Ile His Met Ile Leu Lys Lys Gly Ser Glu Ser Cys
            100                 105                 110
Asn Leu Phe Leu Lys Ser Leu Lys Glu Trp Asn Tyr Pro Leu Phe Gln
        115                 120                 125
Asp Leu Asn Gly Gln Ser Leu Phe His Gln Thr Ser Glu Gly Asp Leu
    130                 135                 140
Asp Asp Leu Ala Gln Asp Leu Lys Asp Leu Tyr His Thr Pro Ser Phe
145                 150                 155                 160
Leu Asn Phe Tyr Pro Leu Gly Glu Asp Ile Asp Ile Ile Phe Asn Leu
                165                 170                 175
Lys Ser Thr Phe Thr Glu Pro Val Leu Trp Arg Lys Asp Gln His His
            180                 185                 190
His Arg Val Glu Gln Leu Thr Leu Asn Gly Leu Leu Gln Ala Leu Gln
        195                 200                 205
Ser Pro Cys Ile Ile Glu Gly Glu Ser Gly Lys Gly Lys Ser Thr Leu
    210                 215                 220
Leu Gln Arg Ile Ala Met Leu Trp Gly Ser Gly Lys Cys Lys Ala Leu
225                 230                 235                 240
Thr Lys Phe Lys Phe Val Phe Phe Leu Arg Leu Ser Arg Ala Gln Gly
                245                 250                 255
Gly Leu Phe Glu Thr Leu Cys Asp Gln Leu Leu Asp Ile Pro Gly Thr
            260                 265                 270
Ile Arg Lys Gln Thr Phe Met Ala Met Leu Leu Lys Leu Arg Gln Arg
        275                 280                 285
Val Leu Phe Leu Leu Asp Gly Tyr Asn Glu Phe Lys Pro Gln Asn Cys
    290                 295                 300
Pro Glu Ile Glu Ala Leu Ile Lys Glu Asn His Arg Phe Lys Asn Met
305                 310                 315                 320
Val Ile Val Thr Thr Thr Thr Glu Cys Leu Arg His Ile Arg Gln Phe
                325                 330                 335
```

Gly Ala Leu Thr Ala Glu Val Gly Asp Met Thr Glu Asp Ser Ala Gln
340 345 350
Ala Leu Ile Arg Glu Val Leu Ile Lys Glu Leu Ala Glu Gly Leu Leu
355 360 365
Leu Gln Ile Gln Lys Ser Arg Cys Leu Arg Asn Leu Met Lys Thr Pro
370 375 380
Leu Phe Val Val Ile Thr Cys Ala Ile Gln Met Gly Glu Ser Glu Phe
385 390 395 400
His Ser His Thr Gln Thr Thr Leu Phe His Thr Phe Tyr Asp Leu Leu
405 410 415
Ile Gln Lys Asn Lys His Lys His Lys Gly Val Ala Ala Ser Asp Phe
420 425 430
Ile Arg Ser Leu Asp His Cys Gly Asp Leu Ala Leu Glu Gly Val Phe
435 440 445
Ser His Lys Phe Asp Phe Glu Leu Gln Asp Val Ser Ser Val Asn Glu
450 455 460
Asp Val Leu Leu Thr Thr Gly Leu Leu Cys Lys Tyr Thr Ala Gln Arg
465 470 475 480
Phe Lys Pro Lys Tyr Lys Phe Phe His Lys Ser Phe Gln Glu Tyr Thr
485 490 495
Ala Gly Arg Arg Leu Ser Ser Leu Leu Thr Ser His Glu Pro Glu Glu
500 505 510
Val Thr Lys Gly Asn Gly Tyr Leu Gln Lys Met Val Ser Ile Ser Asp
515 520 525
Ile Thr Ser Thr Tyr Ser Ser Leu Leu Arg Tyr Thr Cys Gly Ser Ser
530 535 540
Val Glu Ala Thr Arg Ala Val Met Lys His Leu Ala Ala Val Tyr Gln
545 550 555 560
His Gly Cys Leu Leu Gly Leu Ser Ile Ala Lys Arg Pro Leu Trp Arg
565 570 575
Gln Glu Ser Leu Gln Ser Val Lys Asn Thr Thr Glu Gln Glu Ile Leu
580 585 590
Lys Ala Ile Asn Ile Asn Ser Phe Val Glu Cys Gly Ile His Leu Tyr
595 600 605
Gln Glu Ser Thr Ser Lys Ser Ala Leu Ser Gln Glu Phe Glu Ala Phe
610 615 620
Phe Gln Gly Lys Ser Leu Tyr Ile Asn Ser Gly Asn Ile Pro Asp Tyr
625 630 635 640
Leu Phe Asp Phe Phe Glu His Leu Pro Asn Cys Ala Ser Ala Leu Asp
645 650 655
Phe Ile Lys Leu Asp Phe Tyr Gly Gly Ala Met Ala Ser Trp Glu Lys
660 665 670

```
Ala Ala Glu Asp Thr Gly Gly Ile His Met Glu Glu Ala Pro Glu Thr
        675                 680                 685
Tyr Ile Pro Ser Arg Ala Val Ser Leu Phe Phe Asn Trp Lys Gln Glu
    690                 695                 700
Phe Arg Thr Leu Glu Val Thr Leu Arg Asp Phe Ser Lys Leu Asn Lys
705                 710                 715                 720
Gln Asp Ile Arg Tyr Leu Gly Lys Ile Phe Ser Ser Ala Thr Ser Leu
                725                 730                 735
Arg Leu Gln Ile Lys Arg Cys Ala Gly Val Ala Gly Ser Leu Ser Leu
            740                 745                 750
Val Leu Ser Thr Cys Lys Asn Ile Tyr Ser Leu Met Val Glu Ala Ser
        755                 760                 765
Pro Leu Thr Ile Glu Asp Glu Arg His Ile Thr Ser Val Thr Asn Leu
    770                 775                 780
Lys Thr Leu Ser Ile His Asp Leu Gln Asn Gln Arg Leu Pro Gly Gly
785                 790                 795                 800
Leu Thr Asp Ser Leu Gly Asn Leu Lys Asn Leu Thr Lys Leu Ile Met
                805                 810                 815
Asp Asn Ile Lys Met Asn Glu Glu Asp Ala Ile Lys Leu Ala Glu Gly
            820                 825                 830
Leu Lys Asn Leu Lys Lys Met Cys Leu Phe His Leu Thr His Leu Ser
        835                 840                 845
Asp Ile Gly Glu Gly Met Asp Tyr Ile Val Lys Ser Leu Ser Ser Glu
    850                 855                 860
Pro Cys Asp Leu Glu Glu Ile Gln Leu Val Ser Cys Cys Leu Ser Ala
865                 870                 875                 880
Asn Ala Val Lys Ile Leu Ala Gln Asn Leu His Asn Leu Val Lys Leu
                885                 890                 895
Ser Ile Leu Asp Leu Ser Glu Asn Tyr Leu Glu Lys Asp Gly Asn Glu
            900                 905                 910
Ala Leu His Glu Leu Ile Asp Arg Met Asn Val Leu Glu Gln Leu Thr
        915                 920                 925
Ala Leu Met Leu Pro Trp Gly Cys Asp Val Gln Gly Ser Leu Ser Ser
    930                 935                 940
Leu Leu Lys His Leu Glu Glu Val Pro Gln Leu Val Lys Leu Gly Leu
945                 950                 955                 960
Lys Asn Trp Arg Leu Thr Asp Thr Glu Ile Arg Ile Leu Gly Ala Phe
                965                 970                 975
Phe Gly Lys Asn Pro Leu Lys Asn Phe Gln Gln Leu Asn Leu Ala Gly
            980                 985                 990
Asn Arg Val Ser Ser Asp Gly Trp Leu Ala Phe Met Gly Val Phe Glu
        995                 1000                1005
```

```
Asn Leu Lys Gln Leu Val Phe Phe Asp Phe Ser Thr Lys Glu Phe Leu
    1010                1015                1020
Pro Asp Pro Ala Leu Val Arg Lys Leu Ser Gln Val Leu Ser Lys Leu
1025                1030                1035                104
Thr Phe Leu Gln Glu Ala Arg Leu Val Gly Trp Gln Phe Asp Asp Asp
                1045                1050                1055
Asp Leu Ser Val Ile Thr Gly Ala Phe Lys Leu Val Thr Ala
            1060                1065                1070
```

<210> 50
<211> 487
<212> PRT
<213> Homo sapiens

<400> 50

```
Met Pro Pro Leu Pro Gln Trp Ser Phe Pro Arg Pro Asp His Cys His
 1               5                  10                  15
Val Thr Phe Val Thr Leu Lys Cys Asp Ser Ser Lys Lys Arg Arg Arg
            20                  25                  30
Gly Arg Lys Ser Pro Ser Lys Glu Val Ser His Ile Thr Ala Glu Phe
        35                  40                  45
Glu Ile Glu Thr Lys Met Glu Glu Ala Ser Asp Thr Cys Glu Ala Asp
    50                  55                  60
Cys Leu Arg Lys Arg Ala Glu Gln Ser Leu Gln Ala Ala Ile Lys Thr
65                  70                  75                  80
Leu Arg Lys Ser Ile Gly Arg Gln Gln Phe Tyr Val Gln Val Ser Gly
                85                  90                  95
Thr Glu Tyr Glu Val Ala Gln Arg Pro Ala Lys Ala Leu Glu Gly Gln
            100                 105                 110
Gly Ala Cys Gly Ala Gly Gln Val Leu Gln Asp Ser Lys Cys Val Ala
        115                 120                 125
Cys Gly Pro Gly Thr His Phe Gly Gly Glu Leu Gly Gln Cys Val Ser
    130                 135                 140
Cys Met Pro Gly Thr Tyr Gln Asp Met Glu Gly Gln Leu Ser Cys Thr
145                 150                 155                 160
Pro Cys Pro Ser Ser Asp Gly Leu Gly Leu Pro Gly Ala Arg Asn Val
                165                 170                 175
Ser Glu Cys Gly Gly Lys Cys Gly Pro Arg Arg Arg Gly Phe Phe Ser
            180                 185                 190
Ala Asp Gly Phe Lys Pro Cys Gln Ala Cys Pro Val Gly Thr Tyr Gln
        195                 200                 205
Pro Glu Pro Gly Arg Thr Gly Cys Phe Pro Cys Gly Gly Gly Leu Leu
```

```
    210                 215                 220
Thr Lys His Glu Gly Thr Thr Ser Phe Gln Asp Cys Glu Ala Lys Val
225                 230                 235                 240
His Cys Ser Pro Gly His His Tyr Asn Thr Thr Thr His Arg Cys Ile
                245                 250                 255
Arg Cys Pro Val Gly Thr Tyr Gln Pro Glu Phe Gly Gln Asn His Cys
            260                 265                 270
Ile Thr Cys Pro Gly Asn Thr Ser Thr Asp Phe Asp Gly Ser Thr Asn
        275                 280                 285
Val Thr His Cys Lys Asn Gln His Cys Gly Gly Glu Leu Gly Asp Tyr
    290                 295                 300
Thr Gly Tyr Ile Glu Ser Pro Asn Tyr Pro Gly Asp Tyr Pro Ala Asn
305                 310                 315                 320
Ala Glu Cys Val Trp His Ile Ala Pro Pro Pro Lys Arg Arg Ile Leu
                325                 330                 335
Ile Val Val Pro Glu Ile Phe Leu Pro Ile Glu Asp Glu Cys Gly Asp
            340                 345                 350
Val Leu Val Met Arg Lys Ser Ala Ser Pro Thr Ser Ile Thr Thr Tyr
        355                 360                 365
Glu Thr Cys Gln Thr Tyr Glu Arg Pro Ile Ala Phe Thr Ser Arg Ser
    370                 375                 380
Arg Lys Leu Trp Ile Gln Phe Lys Ser Asn Glu Gly Asn Ser Gly Lys
385                 390                 395                 400
Gly Phe Gln Val Pro Tyr Val Thr Tyr Asp Glu Asp Tyr Gln Gln Leu
                405                 410                 415
Ile Glu Asp Ile Val Arg Asp Gly Arg Leu Tyr Ala Ser Glu Asn His
            420                 425                 430
Gln Glu Ile Leu Lys Asp Lys Lys Leu Ile Lys Ala Leu Phe Asp Val
        435                 440                 445
Leu Ala His Pro Gln Asn Tyr Phe Lys Tyr Thr Ala Gln Glu Ser Lys
    450                 455                 460
Glu Met Phe Pro Arg Ser Phe Ile Lys Leu Leu Arg Ser Lys Val Ser
465                 470                 475                 480
Arg Phe Leu Arg Pro Tyr Lys
                485
```

<210> 51
<211> 965
<212> PRT
<213> Homo sapiens

<400> 51

```
Met Gly Ala Ala Ala Val Arg Trp His Leu Cys Val Leu Leu Ala Leu
 1               5                  10                  15
Gly Thr Arg Gly Arg Leu Ala Gly Gly Ser Gly Leu Pro Gly Ser Val
            20                  25                  30
Asp Val Asp Glu Cys Ser Glu Gly Thr Asp Asp Cys His Ile Asp Ala
        35                  40                  45
Ile Cys Gln Asn Thr Pro Lys Ser Tyr Lys Cys Leu Cys Lys Pro Gly
    50                  55                  60
Tyr Lys Gly Glu Gly Lys Gln Cys Glu Asp Ile Asp Glu Cys Glu Asn
65                  70                  75                  80
Asp Tyr Tyr Asn Gly Gly Cys Val His Glu Cys Ile Asn Ile Pro Gly
                85                  90                  95
Asn Tyr Arg Cys Thr Cys Phe Asp Gly Phe Met Leu Ala His Asp Gly
            100                 105                 110
His Asn Cys Leu Asp Val Asp Glu Cys Gln Asp Asn Asn Gly Gly Cys
        115                 120                 125
Gln Gln Ile Cys Val Asn Ala Met Gly Ser Tyr Glu Cys Gln Cys His
    130                 135                 140
Ser Gly Phe Phe Leu Ser Asp Asn Gln His Thr Cys Ile His Arg Ser
145                 150                 155                 160
Asn Glu Gly Met Asn Cys Met Asn Lys Asp His Gly Cys Ala His Ile
                165                 170                 175
Cys Arg Glu Thr Pro Lys Gly Gly Val Ala Cys Asp Cys Arg Pro Gly
            180                 185                 190
Phe Asp Leu Ala Gln Asn Gln Lys Asp Cys Thr Leu Thr Cys Asn Tyr
        195                 200                 205
Gly Asn Gly Gly Cys Gln His Ser Cys Glu Asp Thr Asp Thr Gly Pro
    210                 215                 220
Thr Cys Gly Cys His Gln Lys Tyr Ala Leu His Ser Asp Gly Arg Thr
225                 230                 235                 240
Cys Ile Glu Thr Cys Ala Val Asn Asn Gly Gly Cys Asp Arg Thr Cys
                245                 250                 255
Lys Asp Thr Ala Thr Gly Val Arg Cys Ser Cys Pro Val Gly Phe Thr
            260                 265                 270
Leu Gln Pro Asp Gly Lys Thr Cys Lys Asp Ile Asn Glu Cys Leu Val
        275                 280                 285
Asn Asn Gly Gly Cys Asp His Phe Cys Arg Asn Thr Val Gly Ser Phe
    290                 295                 300
Glu Cys Gly Cys Arg Lys Gly Tyr Lys Leu Leu Thr Asp Glu Arg Thr
305                 310                 315                 320
Cys Gln Asp Ile Asp Glu Cys Ser Phe Glu Arg Thr Cys Asp His Ile
                325                 330                 335
```

```
Cys Ile Asn Ser Pro Gly Ser Phe Gln Cys Leu Cys His Arg Gly Tyr
            340                 345                 350
Ile Leu Tyr Gly Thr Thr His Cys Gly Asp Val Asp Glu Cys Ser Met
        355                 360                 365
Ser Asn Gly Ser Cys Asp Gln Gly Cys Val Asn Thr Lys Gly Ser Tyr
    370                 375                 380
Glu Cys Val Cys Pro Pro Gly Arg Arg Leu His Trp Asn Gly Lys Asp
385                 390                 395                 400
Cys Val Glu Thr Gly Lys Cys Leu Ser Arg Ala Lys Thr Ser Pro Arg
                405                 410                 415
Ala Gln Leu Ser Cys Ser Lys Ala Gly Gly Val Glu Ser Cys Phe Leu
            420                 425                 430
Ser Cys Pro Ala His Thr Leu Phe Val Pro Asp Ser Glu Asn Ser Tyr
        435                 440                 445
Val Leu Ser Cys Gly Val Pro Gly Pro Gln Gly Lys Ala Leu Gln Lys
    450                 455                 460
Arg Asn Gly Thr Ser Ser Gly Leu Gly Pro Ser Cys Ser Asp Ala Pro
465                 470                 475                 480
Thr Thr Pro Ile Lys Gln Lys Ala Arg Phe Lys Ile Arg Asp Ala Lys
                485                 490                 495
Cys His Leu Arg Pro His Ser Gln Ala Arg Ala Lys Glu Thr Ala Arg
            500                 505                 510
Gln Pro Leu Leu Asp His Cys His Val Thr Phe Val Thr Leu Lys Cys
        515                 520                 525
Asp Ser Ser Lys Lys Arg Arg Arg Gly Arg Lys Ser Pro Ser Lys Glu
    530                 535                 540
Val Ser His Ile Thr Ala Glu Phe Glu Ile Glu Thr Lys Met Glu Glu
545                 550                 555                 560
Ala Ser Asp Thr Cys Glu Ala Asp Cys Leu Arg Lys Arg Ala Glu Gln
                565                 570                 575
Ser Leu Gln Ala Ala Ile Lys Thr Leu Arg Lys Ser Ile Gly Arg Gln
            580                 585                 590
Gln Phe Tyr Val Gln Val Ser Gly Thr Glu Tyr Glu Val Ala Gln Arg
        595                 600                 605
Pro Ala Lys Ala Leu Glu Gly Gln Gly Ala Cys Gly Ala Gly Gln Val
    610                 615                 620
Leu Gln Asp Ser Lys Cys Val Ala Cys Gly Pro Gly Thr His Phe Gly
625                 630                 635                 640
Gly Glu Leu Gly Gln Cys Val Ser Cys Met Pro Gly Thr Tyr Gln Asp
                645                 650                 655
Met Glu Gly Gln Leu Ser Cys Thr Pro Cys Pro Ser Ser Asp Gly Leu
            660                 665                 670
```

```
Gly Leu Pro Gly Ala Arg Asn Val Ser Glu Cys Gly Gly Gln Cys Ser
        675                 680                 685
Pro Gly Phe Phe Ser Ala Asp Gly Phe Lys Pro Cys Gln Ala Cys Pro
    690                 695                 700
Val Gly Thr Tyr Gln Pro Glu Pro Gly Arg Thr Gly Cys Phe Pro Cys
705                 710                 715                 720
Gly Gly Gly Leu Leu Thr Lys His Glu Gly Thr Thr Ser Phe Gln Asp
                725                 730                 735
Cys Glu Ala Lys Val His Cys Ser Pro Gly His His Tyr Asn Thr Thr
            740                 745                 750
Thr His Arg Cys Ile Arg Cys Pro Val Gly Thr Tyr Gln Pro Glu Phe
        755                 760                 765
Gly Gln Asn His Cys Ile Thr Cys Pro Gly Asn Thr Ser Thr Asp Phe
    770                 775                 780
Asp Gly Ser Thr Asn Val Thr His Cys Lys Asn Gln His Cys Gly Gly
785                 790                 795                 800
Glu Leu Gly Asp Tyr Thr Gly Tyr Ile Glu Ser Pro Asn Tyr Pro Gly
                805                 810                 815
Asp Tyr Pro Ala Asn Ala Glu Cys Val Trp His Ile Ala Pro Pro Pro
            820                 825                 830
Lys Arg Arg Ile Leu Ile Val Val Pro Glu Ile Phe Leu Pro Ile Glu
        835                 840                 845
Asp Glu Cys Gly Asp Val Leu Val Met Arg Lys Ser Ala Ser Pro Thr
    850                 855                 860
Ser Ile Thr Thr Tyr Glu Thr Cys Gln Thr Tyr Glu Arg Pro Ile Ala
865                 870                 875                 880
Phe Thr Ser Arg Ser Arg Lys Leu Trp Ile Gln Phe Lys Ser Asn Glu
                885                 890                 895
Gly Asn Ser Gly Lys Gly Phe Gln Val Pro Tyr Val Thr Tyr Asp Gly
            900                 905                 910
Lys Ile His Cys Leu His Gly Pro Leu Cys Thr Ala Gln Ala Gly Pro
        915                 920                 925
Trp Arg His Arg Asp Glu Ser His Val Pro Ala Pro Ser Gly Ser Cys
    930                 935                 940
Asp Leu Ala Gly Thr Asp Leu Glu Ala Glu Arg Thr Leu Ser Gly Ala
945                 950                 955                 960
Arg Ala Arg Gln Ala
                965
```

<210> 52
<211> 716
<212> PRT

<213> Homo sapiens

<400> 52

```
Met Ala Arg Met Ser Phe Val Ile Ala Ala Cys Gln Leu Val Leu Gly
 1               5                  10                  15
Leu Leu Met Thr Ser Leu Thr Glu Ser Ser Ile Gln Asn Ser Glu Cys
            20                  25                  30
Pro Gln Leu Cys Val Cys Glu Ile Arg Pro Trp Phe Thr Pro Gln Ser
        35                  40                  45
Thr Tyr Arg Glu Ala Thr Thr Val Asp Cys Asn Asp Leu Arg Leu Thr
    50                  55                  60
Arg Ile Pro Ser Asn Leu Ser Ser Asp Thr Gln Val Leu Leu Leu Gln
65                  70                  75                  80
Ser Asn Asn Ile Ala Lys Thr Val Asp Glu Leu Gln Gln Leu Phe Asn
                85                  90                  95
Leu Thr Glu Leu Asp Phe Ser Gln Asn Asn Phe Thr Asn Ile Lys Glu
            100                 105                 110
Val Gly Leu Ala Asn Leu Thr Gln Leu Thr Thr Leu His Leu Glu Glu
        115                 120                 125
Asn Gln Ile Thr Glu Met Thr Asp Tyr Cys Leu Gln Asp Leu Ser Asn
    130                 135                 140
Leu Gln Glu Leu Tyr Ile Asn His Asn Gln Ile Ser Thr Ile Ser Ala
145                 150                 155                 160
His Ala Phe Ala Gly Leu Lys Asn Leu Leu Arg Leu His Leu Asn Ser
                165                 170                 175
Asn Lys Leu Lys Val Ile Asp Ser Arg Trp Phe Asp Ser Thr Pro Asn
            180                 185                 190
Leu Glu Ile Leu Met Ile Gly Glu Asn Pro Val Ile Gly Ile Leu Asp
        195                 200                 205
Met Asn Phe Lys Pro Leu Ala Asn Leu Arg Ser Leu Val Leu Ala Gly
    210                 215                 220
Met Tyr Leu Thr Asp Ile Pro Gly Asn Ala Leu Val Gly Leu Asp Ser
225                 230                 235                 240
Leu Glu Ser Leu Ser Phe Tyr Asp Asn Lys Leu Val Lys Val Pro Gln
                245                 250                 255
Leu Ala Leu Gln Lys Val Pro Asn Leu Lys Phe Leu Asp Leu Asn Lys
            260                 265                 270
Asn Pro Ile His Lys Ile Gln Glu Gly Asp Phe Lys Asn Met Leu Arg
        275                 280                 285
Leu Lys Glu Leu Gly Ile Asn Asn Met Gly Glu Leu Val Ser Val Asp
    290                 295                 300
Arg Tyr Ala Leu Asp Asn Leu Pro Glu Leu Thr Lys Leu Glu Ala Thr
```

305 310 315 320
Asn Asn Pro Lys Leu Ser Tyr Ile His Arg Leu Ala Phe Arg Ser Val
325 330 335
Pro Ala Leu Glu Ser Leu Met Leu Asn Asn Asn Ala Leu Asn Ala Ile
340 345 350
Tyr Gln Lys Thr Val Glu Ser Leu Pro Asn Leu Arg Glu Ile Ser Ile
355 360 365
His Ser Asn Pro Leu Arg Cys Asp Cys Val Ile His Trp Ile Asn Ser
370 375 380
Asn Lys Thr Asn Ile Arg Phe Met Glu Pro Leu Ser Met Phe Cys Ala
385 390 395 400
Met Pro Pro Glu Tyr Lys Gly His Gln Val Lys Glu Val Leu Ile Gln
405 410 415
Asp Ser Ser Glu Gln Cys Leu Pro Met Ile Ser His Asp Ser Phe Pro
420 425 430
Asn Arg Leu Asn Val Asp Ile Gly Thr Thr Val Phe Leu Asp Cys Arg
435 440 445
Ala Met Ala Glu Pro Glu Pro Glu Ile Tyr Trp Val Thr Pro Ile Gly
450 455 460
Asn Lys Ile Thr Val Glu Thr Leu Ser Asp Lys Tyr Lys Leu Ser Ser
465 470 475 480
Glu Gly Thr Leu Glu Ile Ser Asn Ile Gln Ile Glu Asp Ser Gly Arg
485 490 495
Tyr Thr Cys Val Ala Gln Asn Val Gln Gly Ala Asp Thr Arg Val Ala
500 505 510
Thr Ile Lys Val Asn Gly Thr Leu Leu Asp Gly Thr Gln Val Leu Lys
515 520 525
Ile Tyr Val Lys Gln Thr Glu Ser His Ser Ile Leu Val Ser Trp Lys
530 535 540
Val Asn Ser Asn Val Met Thr Ser Asn Leu Lys Trp Ser Ser Ala Thr
545 550 555 560
Met Lys Ile Asp Asn Pro His Ile Thr Tyr Thr Ala Arg Val Pro Val
565 570 575
Asp Val His Glu Tyr Asn Leu Thr His Leu Gln Pro Ser Thr Asp Tyr
580 585 590
Glu Val Cys Leu Thr Val Ser Asn Ile His Gln Gln Thr Gln Lys Ser
595 600 605
Cys Val Asn Val Thr Thr Lys Asn Ala Ala Phe Ala Val Asp Ile Ser
610 615 620
Asp Gln Glu Thr Ser Thr Ala Leu Ala Ala Val Met Gly Ser Met Phe
625 630 635 640
Ala Val Ile Ser Leu Ala Ser Ile Ala Val Tyr Phe Ala Lys Arg Phe

645 650 655

Lys Arg Lys Asn Tyr His His Ser Leu Lys Lys Tyr Met Gln Lys Thr
660 665 670

Ser Ser Ile Pro Leu Asn Glu Leu Tyr Pro Pro Leu Ile Asn Leu Trp
675 680 685

Glu Gly Asp Ser Glu Lys Asp Lys Asp Gly Ser Ala Asp Thr Lys Pro
690 695 700

Thr Gln Val Asp Thr Ser Arg Ser Tyr Tyr Met Trp
705 710 715

```
Met Tyr Lys Ser Leu Asn Ile Asp Glu Cys Asp Leu His Ala Trp Leu
1               5                  10                  15
Asp Leu Pro Ala Glu Lys Pro Leu Gly Val Val Asn Arg Val Cys Trp
            20                  25                  30
Gly Phe Ile Arg Phe Lys Gly Tyr Met Tyr Pro Leu Asp Tyr Leu Asn
        35                  40                  45
Phe Lys Asp Asn Ser Arg Ala Leu Ile Gln Arg Met Gly Met Thr
    50                  55                  60
Val Ile Lys Gln Ile Thr Asp Phe Val Trp Asn Val Leu Asn
65                  70                  75                  80
Arg Glu Glu Val Asn Ile Ile Cys Cys Glu Lys Val Glu Gln Asp Ala
                85                  90                  95
Ala Arg Gly Ile Ile His Met Ile Leu Lys Lys Gly Ser Glu Cys Ser
            100                 105                 110
Asn Leu Phe Leu Lys Ser Leu Lys Glu Trp Asn Tyr Pro Leu Phe Gln
        115                 120                 125
Asp Leu Asn Gly Gln Ser Leu Phe His Gln Thr Ser Glu Gly Asp Leu
    130                 135                 140
Asp Asp Leu Ala Gln Asp Leu Lys Asp Leu Tyr His Thr Pro Ser Phe
145                 150                 155                 160
Leu Asn Phe Tyr Pro Leu Gly Glu Asp Ile Asp Ile Ile Phe Asn Leu
                165                 170                 175
Lys Ser Thr Phe Thr Glu Pro Val Leu Trp Arg Lys Asp Gln His His
            180                 185                 190
His Arg Val Glu Gln Leu Thr Leu Asn Gly Leu Leu Gln Ala Leu Gln
        195                 200                 205
Ser Pro Cys Ile Ile Glu Gly Glu Ser Gly Lys Gly Lys Ser Thr Leu
    210                 215                 220
Leu Gln Arg Ile Ala Met Leu Trp Gly Ser Gly Lys Cys Lys Ala Leu
225                 230                 235                 240
Thr Lys Phe Lys Phe Val Phe Phe Leu Arg Leu Ser Arg Ala Gln Gly
                245                 250                 255
Gly Leu Phe Glu Thr Leu Cys Asp Gln Leu Leu Asp Ile Pro Gly Thr
            260                 265                 270
Gln Thr Phe Met Ala Met Leu Leu Lys Leu Arg Gln Arg
        275                 280                 285
Ile Arg Lys Gln Thr Gly Tyr Asn Glu Phe Lys Pro Gln Asn Cys
    290                 295                 300
Val Leu Phe Leu Leu Asp Gly Tyr Asn His Arg Phe Lys Asn Met
305                 310                 315                 320
Pro Glu Ile Glu Ala Leu Ile Lys Glu Asn His Arg Gln Phe
                325                 330                 335
Val Ile Val Thr Thr Thr Thr Glu Cys Leu Arg His Ile Arg Gln
            340                 345                 350
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Gly Ala Leu Thr Ala Glu Val Gly Asp Met Thr Glu Asp Ser Ala Gln
340 345 350
Ala Leu Ile Arg Glu Val Leu Ile Lys Glu Leu Ala Glu Gly Leu Leu
355 360 365
Leu Gln Ile Gln Lys Ser Arg Cys Leu Arg Asn Leu Met Lys Thr Pro
370 375 380
Leu Phe Val Val Ile Thr Cys Ala Ile Gln Met Gly Glu Ser Glu Phe
385 390 395 400
His Ser His Thr Gln Thr Thr Leu Phe His Thr Phe Tyr Asp Leu Leu
405 410 415
Ile Gln Lys Asn Lys His Lys His Lys Gly Val Ala Ala Ser Asp Phe
420 425 430
Ile Arg Ser Leu Asp His Cys Gly Asp Leu Ala Leu Glu Gly Val Phe
435 440 445
Ser His Lys Phe Asp Phe Glu Leu Gln Asp Val Ser Ser Val Asn Glu
450 455 460
Asp Val Leu Leu Thr Thr Gly Leu Leu Cys Lys Tyr Thr Ala Gln Arg
465 470 475 480
Phe Lys Pro Lys Tyr Lys Phe Phe His Lys Ser Phe Gln Glu Tyr Thr
485 490 495
Ala Gly Arg Arg Leu Ser Ser Leu Leu Thr Ser His Glu Pro Glu Glu
500 505 510
Val Thr Lys Gly Asn Gly Tyr Leu Gln Lys Met Val Ser Ile Ser Asp
515 520 525
Ile Thr Ser Thr Tyr Ser Ser Leu Leu Arg Tyr Thr Cys Gly Ser Ser
530 535 540
Val Glu Ala Thr Arg Ala Val Met Lys His Leu Ala Ala Val Tyr Gln
545 550 555 560
His Gly Cys Leu Leu Gly Leu Ser Ile Ala Lys Arg Pro Leu Trp Arg
565 570 575
Gln Glu Ser Leu Gln Ser Val Lys Asn Thr Thr Glu Gln Glu Ile Leu
580 585 590
Lys Ala Ile Asn Ile Asn Ser Phe Val Glu Cys Gly Ile His Leu Tyr
595 600 605
Gln Glu Ser Thr Ser Lys Ser Ala Leu Ser Gln Glu Phe Glu Ala Phe
610 615 620
Phe Gln Gly Lys Ser Leu Tyr Ile Asn Ser Gly Asn Ile Pro Asp Tyr
625 630 635 640
Leu Phe Asp Phe Phe Glu His Leu Pro Asn Cys Ala Ser Ala Leu Asp
645 650 655
Phe Ile Lys Leu Asp Phe Tyr Gly Gly Ala Met Ala Ser Trp Glu Lys
660 665 670